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Research on the cost-effectiveness of upper digestive endoscopy for the diagnosis of early gastric cancer

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I. **Areia M**, Carvalho R, Cadime AT, Rocha Gonçalves F, Dinis-Ribeiro M.
Screening for Gastric Cancer and Surveillance of Premalignant Lesions: a Systematic Review of Cost-Effectiveness Studies.
Helicobacter 2013; 18: 325-37.

II. Marques-Silva L, **Areia M,** Elvas L, Dinis-Ribeiro M.
Prevalence of Gastric Precancerous Conditions: A Systematic Review and Meta-analysis.
Eur J Gastroenterol Hepatol 2014; 26: 378–87.

III. **Areia M**, Alves S, Brito D, Cadime AT, Carvalho R, Saraiva S, Ferreira S, Moleiro J, Dias Pereira A, Carrasquinho J, Lopes L, Ramada J, Marcos-Pinto R, Pedroto I, Contente L, Eliseu L, Vieira AM, Sampaio M, Sousa HT, Almeida N, Gregório C, Portela F, Sofia C, Braga V, Baginha E, Bana e Costa T, Chagas C, Lebre Mendes L, Magalhães-Costa P, Matos L, Rocha Gonçalves F, Dinis-Ribeiro M.
Health-related Quality of Life and Utilities in Gastric Premalignant Conditions and Malignant Lesions: a Multicentre Study in a High Prevalence Country.
J Gastrointestin Liver Dis December 2014 Vol. 23 No 4.

IV. **Areia M**, Dinis-Ribeiro M, Rocha Gonçalves F.
Cost-utility analysis of endoscopic surveillance of patients with gastric premalignant conditions.
Helicobacter 2014 Aug 28. doi: 10.1111/hel.12150.

Em cumprimento do disposto no referido Decreto-Lei o aluno declara que participou ativamente em todos os trabalhos acima referidos.

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Preamble and Outline of Thesis

Preamble

The focus of research for the present Thesis was to establish the best cost-utility estimate for the Portuguese population on the use of conventional upper endoscopy for the diagnosis of early gastric cancer.

In light of this, our main aim was to perform an economic analysis on the secondary prevention of gastric adenocarcinoma by endoscopic surveillance of patients at high risk of progressing from extensive atrophy or intestinal metaplasia conditions to cancer. The study was designed for the Portuguese population because Portugal has the highest incidence of the disease in Western Europe.

The knowledge obtained from this project is very important for a Portuguese Gastroenterologist that works in an Oncology Institute, not only by answering some unsolved questions in the clinical practice pointed out by recent guidelines, such as follow-up or not patients at-risk, how, when and at what cost, but also allowing to use the obtained know-how in other fields of Gastroenterology.

The results of the study should be of interest at a national level as the prevalence of gastric premalignant conditions is relevant in our country and most gastroenterologists in Portugal perform upper endoscopic exams in their clinical practice.

Furthermore, the results of the model obtained could be replicated in other countries as the clinical model should be applicable in other settings, just needing the proper adjustments on local costs, providing evidence that could be generalized to gastroenterologists worldwide, interested in the problem of gastric cancer.

Along with the four specific studies necessary for the present Thesis, the author also promoted the work in this field by dissemination of proposals publishing an opinion article in an indexed Portuguese journal (Areia, Pimentel-Nunes, Marcos-Pinto, & Dinis-Ribeiro, 2013), promoting the search for the best evidence by publishing an article on quality of endoscopic reporting in Gastroenterology (Areia, Soares, & Dinis-Ribeiro, 2010), participating in a gastric cancer book chapter promoted and published by the Portuguese Medical Association (Marcos-Pinto, Areia, Pimentel-Nunes, & Dinis-Ribeiro, 2013), performing a national multicentre cross-sectional study to assess the prevalence of gastric premalignant conditions and general performance of endoscopy in our country (Areia, Dinis-Ribeiro, & Portuguese Society of Digestive Endoscopy, 2014) and participating as a co-author of the guidelines on the Management of Precancerous conditions and lesions in the Stomach (MAPS) (Dinis-Ribeiro, Areia et al., 2012; Dinis-Ribeiro, Areia et al., 2012).

Outline of Thesis

In Chapter I, the rationale to the subject chosen for the present thesis is presented. A brief introduction on the gastric cancer problem worldwide and specifically in Portugal is offered, along with the available evidence on economic studies on surveillance of premalignant conditions and clinical guidelines recommendations by the time of the thesis origin.

In Chapter II, the background that explains the importance of the gastric cancer theme is presented along with a description of the gastric carcinogenesis cascade assumptions, the relevance of endoscopy for the diagnosis, assessment of extension and surveillance of gastric premalignant conditions and how economic studies are implemented in the medical field taking in consideration the published guidelines for this specific type of studies, justifying our choice on a cost-utility model for the endoscopic surveillance of gastric premalignant conditions.

In Chapter III, the aims of each of the four studies performed along the present thesis are presented.

In Chapter IV, we present the publications that emerged from the present thesis, in its final published format.

In Chapter V, a discussion of all the results of our data is presented. Each result is discussed in comparison with the available evidence and the cost-utility model is also compared with previous similar reports in terms of strength of evidence and dissimilarities.

Finally, in Chapter VI, our thesis conclusions are presented and further research is identified.

Summary

Gastric adenocarcinoma represents a health problem worldwide due to its high incidence and mortality rates being the fourth most common malignancy and the second leading cause of cancer death (Ferlay, Shin et al., 2010). Its prognosis is highly dependent of the stage at diagnosis, that usually occurs in advanced stages, requiring demanding treatments and costs (Hundahl, Phillips, & Menck, 2000). Although being a worldwide problem, different prevalence rates among countries lead to different options; in Japan, universal screening of the population using fluoroscopy is used, followed by conventional endoscopy with biopsies for the positive results (Hamashima, Shibuya et al., 2008) whilst in most other developed countries the low incidence rate makes screening not cost-effective (Hirota, Zuckerman et al., 2006). In Portugal, the incidence rate for gastric cancer is located in-between these two realities and so, it is not straightforward that in our country such a program would be justifiable.

This type of carcinoma develops after years of progression of a benign condition such as non atrophic gastritis that might evolve to premalignant conditions, namely chronic atrophic gastritis and intestinal metaplasia, before the development of dysplasia and invasive cancer (Correa, 1992). Endoscopy is usually the first exam to perform for the diagnosis of these gastric premalignant conditions (Hirota, Zuckerman et al., 2006).

Based on the assumption that chronic gastritis starts in the antrum and then spreads to the corpus in an upward manner so that conditions of the corpus are more extensive and related to more advanced stages, it has been suggested to discriminate this extensive phenotype as it could imply an increased risk of progression to dysplasia and invasive cancer. As so, recent guidelines suggest a 3-yearly endoscopic follow-up for these patients, based on clinical data but with no support from the published

economic studies due to conflicting results (Dinis-Ribeiro, Areia et al., 2012; Dinis-Ribeiro, Areia et al., 2012).

Having Portugal an intermediate-risk population for gastric cancer (GLOBOCAN, 2012), to improve our patients quality of live and overall survival, it is important to improve our rates of early gastric cancer detection in order to achieve more curative treatments by endoscopic resections techniques or detection of invasive cancers in an early stage, treatable with less debilitating treatments.

As so, the objective of the present thesis was to determine the cost-utility of endoscopic surveillance every 3 years of patients with extensive gastric premalignant conditions compared with no surveillance. To accomplish that goal we first performed two systematic reviews and one cross-sectional study in order to obtain the best available clinical data for the Portuguese population and then a cost-utility economic analysis on this hypothesis.

Using a Markov model to compare the two strategies and using a societal perspective, clinical data was collected from the mentioned systematic reviews of the literature, costs from published national data and community utilities derived from the cross-sectional study by using the EuroQol questionnaire in terms of Quality Adjusted Life Years (QALY) (EuroQol, 1990). For the Markov model, the population started at the age of 50, a time horizon was set for 25 years and an annual discount rate of 3% was used for both costs and effectiveness.

The results of the model showed that endoscopic surveillance every 3 years provided an Incremental Cost-Effectiveness Ratio (ICER) of € 18,336 below the adopted threshold of € 36,575 proposed by economic guidelines and this strategy dominated

surveillance every 5 or 10 years. Even when the model was evaluated in sensitivity analysis, only a few utilities proved to be relevant in deterministic analysis, while probabilistic analysis showed that in 78% of simulations the model remained cost-effective.

Thus, the conclusion of this thesis is that endoscopic surveillance of patients with premalignant conditions such as extensive atrophy or intestinal metaplasia, every 3 years, in an intermediate-risk country such as Portugal, is cost-effective.

Resumo

O adenocarcinoma gástrico representa um problema de saúde global devido às suas elevadas taxas de incidência e mortalidade, sendo o quarto tumor maligno mais comum e representando a segunda causa de morte por cancro (Ferlay, Shin et al., 2010). O seu prognóstico é altamente dependente da fase de diagnóstico, que geralmente ocorre em estádios avançados, exigindo tratamentos agressivos com custos económicos relevantes (Hundahl, Phillips, & Menck, 2000). Apesar da dimensão do problema a nível mundial, diferentes taxas de prevalência entre países levam à adoção de diferentes estratégias: no Japão realiza-se o rastreio universal da população por fluoroscopia, seguida pela endoscopia digestiva alta convencional com biópsias para os resultados positivos (Hamashima, Shibuya et al., 2008) enquanto na maioria dos outros países desenvolvidos, as baixas taxas de incidência tornam o rastreio demasiado dispendioso (Hirota, Zuckerman et al., 2006). Em Portugal, a taxa de incidência de cancro gástrico está localizada entre estas duas realidades, não sendo fácil definir no nosso país qual a opção mais custo-eficaz.

Este tipo de carcinoma pode ocorrer após vários anos de progressão de uma condição benigna como seja a gastrite não atrófica, que pode evoluir para condições pré-malignas como a gastrite crónica atrófica ou a metaplasia intestinal, antes do desenvolvimento final de displasia e cancro invasivo (Correa, 1992). A endoscopia é geralmente o primeiro exame a efetuar para o diagnóstico destas condições pré-malignas gástricas (Hirota, Zuckerman et al., 2006).

Com base na assunção que a gastrite crónica atrófica se inicia no antro e pode progredir de forma ascendente para o corpo gástrico, de modo que as condições que afetam o corpo são mais extensas e representam estádios mais avançados da doença,

tem sido sugerido discriminar este fenótipo mais extenso que poderia implicar um risco aumentado de progressão para displasia e cancro invasivo. Assim sendo, recomendações recentes sugerem uma vigilância endoscópica a cada 3 anos destes pacientes, recomendações essas baseadas em dados clínicos mas sem o apoio dos estudos económicos disponíveis devido a resultados discordantes (Dinis-Ribeiro, Areia et al., 2012; Dinis-Ribeiro, Areia et al., 2012).

Tendo Portugal uma população de risco intermediário para cancro gástrico (GLOBOCAN, 2012), para melhorar a taxa de sobrevivência e a qualidade de vida dos pacientes, é importante melhorar os índices de deteção do cancro gástrico precoce, a fim de permitir tratamentos curativos através de técnicas de excisão endoscópica ou a deteção de cancros invasivos em estádios iniciais, passíveis de tratamentos menos debilitantes ou dispendiosos.

Assim sendo, o objetivo da presente tese foi determinar a relação de custo-utilidade da vigilância endoscópica cada 3 anos de pacientes com condições gástricas pré-malignas em comparação com a ausência de vigilância. Para atingir esse objetivo foi realizado inicialmente duas revisões sistemáticas e um estudo transversal, de forma a obter os melhores dados clínicos disponíveis da população portuguesa e, em seguida, uma análise económica de custo-utilidade da nossa hipótese clínica de vigilância endoscópica.

Para tal foi usado um modelo de Markov para comparar as duas estratégias, de uma perspetiva social. Os dados clínicos foram obtidos a partir das revisões sistemáticas referidas, os custos económicos de publicações institucionais nacionais e as utilidades da população portuguesa em termos Anos de Vida Ajustados à Qualidade (QALY)

foram obtidas do estudo transversal efetuado, utilizando o questionário EuroQol (EuroQol, 1990). Para a análise económica a população começa o modelo ao atingir a idade de 50 anos, durante um horizonte temporal de 25 anos e foi utilizada uma taxa de desconto anual de 3% quer para os custos quer para a eficácia.

Os resultados do modelo mostram que a vigilância endoscópica a cada 3 anos condiciona uma relação de custo-efetividade incremental (ICER) de 18 336 €, abaixo do limiar de 36 575 € proposto pelas recomendações económicas e que esta estratégia de vigilância domina as opções de vigilância a cada 5 ou 10 anos. Mesmo quando o modelo foi avaliado em análise de sensibilidade, apenas algumas utilidades mostraram ser relevantes na análise determinística, enquanto a análise probabilística mostrou que em 78% das simulações o modelo permaneceu custo-eficaz.

Assim, a conclusão da presente tese é que a vigilância endoscópica de pacientes com condições gástricas pré-malignas extensas, como sejam a presença de atrofia ou metaplasia intestinal no corpo gástrico, a cada 3 anos e num país de risco intermediário como Portugal, é custo-eficaz.

Chapter I - Rationale

Gastric cancer is a health problem presenting very different degrees of magnitude worldwide. Its' geographical incidence varies considerably, being particularly marked in Eastern Asia, Central and Eastern Europe, and South and Central America and although a decrease in its incidence is being observed, its burden is still unacceptably high (Ferlay, Shin et al., 2010). In Portugal it ranks fifth in cancer deaths and its incidence is the highest in Western Europe (Ferlay, Parkin, & Steliarova-Foucher, 2010).

When cancer is diagnosed so late, patients are offered treatments like surgery, chemotherapy or radiotherapy that are costly, impair quality of life, and still offer a poor prognosis, with an overall 5 year survival rate below 25% (Ferlay, Shin et al., 2010; Hundahl, Phillips, & Menck, 2000; Karim-Kos, de Vries et al., 2008). Specifically in Portugal, gastric cancer is a neoplasm with a high incidence rate and most cases also present in advanced stages conducting to poor prognosis.

To prevent late detection of the disease, health authorities should choose between primary prevention programs such as *Helicobacter pylori* (*H. pylori*) screening and eradication to prevent the biologic evolution from normal gastric mucosa to premalignant conditions and to invasive cancer or secondary prevention programmes like population screening or surveillance of patients at high risk for the development of the disease to allow gastric cancer detection in earlier stages with more favourable survival, preferably supported by economic analysis for the strategy adopted (Areia, Carvalho, Cadime, Rocha Goncalves, & Dinis-Ribeiro, 2013; Dinis-Ribeiro, Areia et al., 2012; Dinis-Ribeiro, Areia et al., 2012; Malfertheiner, Megraud et al., 2012). Secondary prevention is usually based on endoscopy because it is widely available, accurate, involves relatively minor invasiveness and offers the chance of simultaneously

performing diagnostic biopsies and/or therapeutic procedures (Hirota, Zuckerman et al., 2006).

This choice of a screening or surveillance strategy depends on the incidence of the disease and while in Japan endoscopic screening is considered cost-effective, in most countries the balance between endoscopic costs and gastric cancer treatment gains renders screening not cost-effective (Areia, Pimentel-Nunes, Marcos-Pinto, & Dinis-Ribeiro, 2013; Dinis-Ribeiro, Areia et al., 2012; Dinis-Ribeiro, Areia et al., 2012; Hamashima, Shibuya et al., 2008).

The intestinal subtype of gastric adenocarcinoma is known to be preceded by a cascade of premalignant conditions and lesions, namely chronic atrophic gastritis, intestinal metaplasia and gastric dysplasia (Correa, 1988; Lauren, 1965) and several different classifications exist for their histological classification (Capelle, de Vries et al., 2010; Dixon, Genta, Yardley, & Correa, 1996; Rugge, Correa et al., 2002; Rugge, Meggio et al., 2007). One reason for this late detection in advanced stages of disease might be the fact that, until 2012, there were no international recommendations to guide clinicians in their care of individuals with these changes and this lead to a wide heterogeneity of practice and failure to diagnose patients with curable forms of cancer in most countries (de Vries, van Grieken et al., 2008; Dinis-Ribeiro, Lopes, da Costa-Pereira, & Moreira-Dias, 2008).

Based on the assumption that chronic gastritis starts in the antrum and then spreads to the corpus in an upward manner so that conditions of the corpus are more extensive and related to more advanced stages, it has been suggested to discriminate this extensive phenotype at an increased risk of progression to dysplasia and invasive

cancer (Dinis-Ribeiro, Areia et al., 2012). The surveillance of patients with these lesions might allow the endoscopic treatment of dysplastic lesions or the detection of early invasive cancers that are treatable with less demanding and cheaper treatments with better prognosis (Correa, 1992; Dinis-Ribeiro, Lopes et al., 2004; Dinis-Ribeiro, Pimentel-Nunes et al., 2009; NCCN, 2013).

Recently published guidelines suggested a 3-yearly endoscopic surveillance for the follow-up of patients with high risk conditions of progression, such as the presence of extensive atrophy or intestinal metaplasia (Dinis-Ribeiro, Areia et al., 2012; Dinis-Ribeiro, Areia et al., 2012) but only three studies have been published so far on the subject.

These three studies published on the surveillance of patients with extensive conditions reported conflicting results on the cost-effectiveness of this option: one concluding on the cost-effectiveness of annual surveillance of these patients but the other two providing incremental cost-effectiveness ratios above the accepted threshold, probably related to different assumptions on rates of progression of these conditions (Dinis-Ribeiro, da Costa-Pereira, Lopes, & Moreira-Dias, 2007; Hassan, Zullo et al., 2010; Yeh, Hur, Kuntz, Ezzati, & Goldie, 2010).

One of these studies represents the only cost-effectiveness study ever conducted on the gastric cancer issue in Portugal, and consisted of a specific endoscopic technology (magnification chromoendoscopy) on a yearly basis for patients at-risk for gastric cancer (patients with chronic atrophic gastritis and intestinal metaplasia) (Dinis-Ribeiro, da Costa-Pereira, Lopes, & Moreira-Dias, 2007). For the use of conventional upper endoscopy on a 3-yearly surveillance protocol for high-risk patients as suggested

from the guidelines, no such study was ever conducted raising the need for the present research.

Chapter II - Background

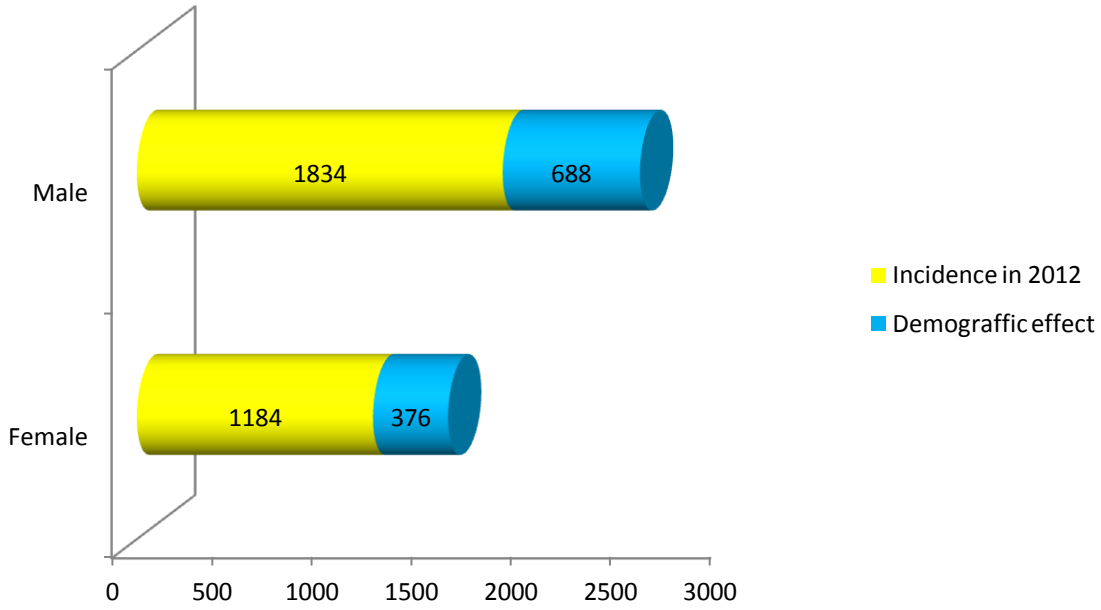
Gastric cancer burden

Gastric cancer is a worldwide problem due to its high mortality as in most cases patients present in advanced stages of the disease. It is the fourth most common malignancy and the second leading cause of cancer death just after lung cancer representing 9.7% of the total mortality with a estimated number of 990,000 new cases per year and 738,000 deaths (Ferlay, Shin et al., 2010) and although a decrease in its incidence is being observed (it ranked first worldwide in 1975), its burden is still unacceptably high (Ferlay, Shin et al., 2010; Parkin, Stjernsward, & Muir, 1984).

In Portugal it ranks fifth in cancer deaths and its incidence is the highest in Western Europe with 3,018 cancers diagnosed in 2012 (Ferlay, Parkin, & Steliarova-Foucher, 2010; GLOBOCAN, 2012).

Most cases are related to infection with *Helicobacter pylori* and other environmental agents and so incidence increases with age. Due to the expected increase aging of populations, namely in Portugal, the estimates for the next 20 years will have an increase in incidence and mortality compared to the present time, empathising the burden of this disease for the next decades (GLOBOCAN, 2012) **(Figure 1)**.

Figure 1 Incidence of gastric cancer in Portugal in 2012 and expected rate for the year 2035, according to the GLOBOCAN estimates



Legend: Gastric cancer cases in Portugal (GLOBOCAN, 2012). The bars in yellow represent the incidence cases in 2012, per gender, while the bars in blue represent the estimated increase by 2035 due to the increasing effect of age in the Portuguese population.

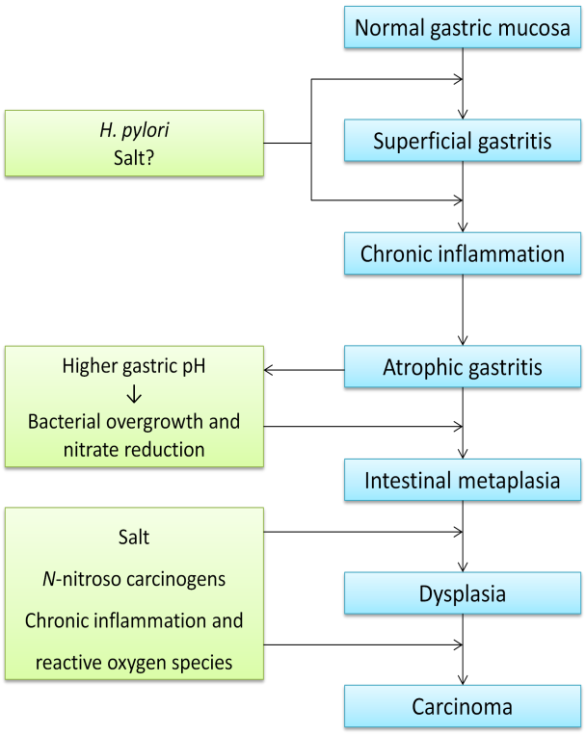
Progression of gastric premalignant conditions and lesions to invasive cancer

Gastric cancer is a disease that embraces several histological types but most cases are represented by the adenocarcinoma type that rises from the mucosal layer and among these, there are two types with very distinct clinical, morphological e prognostic characteristics (Abrams & Wang, 2010).

The intestinal subtype represents more than 95% of all adenocarcinoma, usually comes above the age of 50 years, is highly related to environmental factors namely infection with *H. pylori* and dietary risk factors, is the predominant form in countries with a high incidence of gastric cancer and is the final stage of a progression along many years of a cascade of premalignant conditions such as atrophy or intestinal metaplasia that might evolve to malignant non invasive lesions with dysplasia and finally to invasive cancer. The diffuse type represents less than 5% of cases, most of the times diagnosed before the age of 50, is related to genetic factors namely mutation in the gene CDH1 which encodes the cell adhesion molecule E-cadherin, lacks glandular structure and consists of poorly cohesive cells that infiltrate the wall of the stomach and has a rapid progression to invasiveness and spread to other organs, conditioning a usually worse prognosis (Carneiro, Machado, Seruca, & Sobrinho-Simoes, 1999; Carneiro, Oliveira, Suriano, & Seruca, 2008; Guilford, Hopkins et al., 1998; Lynch, Kaurah et al., 2008; Machado, Oliveira et al., 2001; Machado, Soares et al., 1999; Oliveira, Ferreira et al., 2004).

The most common intestinal type of adenocarcinoma has its prevalence related to male gender, increasing age and high prevalence regions, indicating environmental factors as risk factors for the disease. The accepted model for development of this type of cancer involves a cascade of premalignant conditions occurring over several years, due to environmental and host factors, which might progress to malignant non invasive lesions and invasive cancer (Carneiro, Machado et al., 2001; Correa, 1992; Fox & Wang, 2007; Ihamaki, Saukkonen, & Siurala, 1978). This model is also known as the Correa cascade of gastric carcinogenesis (Correa, 1992) **(Figure 2)**:

Figure 2 Correa cascade of gastric carcinogenesis



Legend: Correa pathway of pathologic events in gastric adenocarcinoma (Fox & Wang, 2007). The normal mucosa, over a long period of time (several years) and due to the exposure to environmental and increased susceptibility due to host factors, might evolve to inflammation that will allow the development of premalignant conditions (atrophy and intestinal metaplasia) occurring in a cascade which might progress to malignant non invasive lesions (dysplasia) and invasive cancer.

Several observational studies have shown that environmental factors play a part and salt, nitrates, tobacco and *H. pylori* are the most fully described agents. *H. pylori* is the single main risk factor and considered to promote the development of these precursor conditions and lesions (Marshall & Warren, 1984). The first of these may be gastric

inflammation that progresses to loss of appropriate glands (atrophy), replacement of original glands with intestinal metaplasia glands that might develop into dysplasia and finally into invasive carcinoma.

Helicobacter pylori infection was first considered a class I carcinogen at the International Agency on Research for Cancer in 1994 and is a chief risk factor for the intestinal type of gastric cancer (IARC, 1994). It is initially acquired in the childhood and it is believed to cause an inflammation that might proceed to more advanced conditions and ultimately to invasive cancer (Banatvala, Mayo et al., 1993; Uemura, Okamoto et al., 2001). Overall, *H. pylori* infected patients are at risk for development of chronic atrophic gastritis and patients who are genetically predisposed to develop atrophy in response to *H. pylori* infection are the ones who are predisposed to gastric cancer (Abrams & Wang, 2010; Correa, Haenszel et al., 1990; Kuipers, 1998).

Chronic inflammation can lead to atrophy and intestinal metaplasia and both confer risk for the development of gastric cancer as they constitute the background in which dysplasia and invasive adenocarcinoma develop (Asaka, Sugiyama et al., 2001; Genta, 1998; Kuipers, Uyterlinde et al., 1995; Rokkas, Filipe, & Sladen, 1991). Rates of progression to atrophy and intestinal metaplasia in patients with chronic gastritis vary widely among studies, ranging between 0.5% to 1.8 % and 0% to 10%, per year, respectively but overall, the gastric cancer risk is too low to justify endoscopic surveillance in all patients with these lesions (Dinis-Ribeiro, Areia et al., 2012; Kuipers, Uyterlinde et al., 1995).

In the clinical setting, severity of atrophy and intestinal metaplasia should be graded and incorporated into scales developed for that purpose, such as the updated Sidney system (combining topographic, morphological and etiological information) (Dixon, Genta, Yardley, & Correa, 1996). Although intra and inter observer agreement is better for intestinal metaplasia than for atrophy, both have low rates of correlation and are difficult to translate to a clinically meaningful score. As so, another appealing alternative is to use the extension of atrophy or intestinal metaplasia among the gastric mucosa to define a subgroup of patients harbouring a higher risk for progression to cancer.

When considering that their topographic extension in the gastric mucosa is relevant, patients presenting with atrophy or intestinal metaplasia in the corpus could represent a subgroup of higher risk patients for whom a specific surveillance programme is recommended (Kuipers & Siersema, 2004). The successors of the updated Sydney System such as the OLGA (Operative Link for Gastritis Assessment) (Rugge, de Boni et al., 2010; Rugge, Meggio et al., 2007; Satoh, Osawa et al., 2008) and the OLGIM systems (Operative Link on Gastric Intestinal Metaplasia) (Capelle, de Vries et al., 2010; Rugge, Fassan et al., 2011) accomplish this objective by incorporating not only the grade but also the extension of atrophy or intestinal metaplasia, respectively. They require that biopsies taken from the gastric mucosa during endoscopy are collected in separate containers from the antrum and the corpus and the histological report can them define grades 3 or above of atrophy or intestinal metaplasia extension that represents those patients with extensive conditions where endoscopic surveillance might be justified. **Table 1** and **table 2** represent the OLGA and the OLGIM grading systems:

Table 1 The OLGA system (Operative Link for Gastritis Assessment)

		Corpus			
	Atrophy score	**No atrophy (Score 0)**	**Mild atrophy (Score 1)**	**Moderate atrophy (Score 2)**	**Severe atrophy (Score 3)**
Antrum *(including incisura angularis)*	**No atrophy (score 0)**	**Stage 0**	**Stage I**	**Stage II**	**Stage II**
	Mild atrophy (score 1)	**Stage I**	**Stage I**	**Stage II**	**Stage III**
	Moderate atrophy (score 2)	**Stage II**	**Stage II**	**Stage III**	**Stage IV**
	Severe atrophy (score 3)	**Stage III**	**Stage III**	**Stage IV**	**Stage IV**

Legend: The Operative Link for Gastritis Assessment table by combining information on atrophy in both the antrum and corpus (Rugge, Meggio et al., 2007). Biopsies from the antrum and corpus should be evaluated for the presence and severity of atrophy in separate, providing a 2x2 table and defining five stages of atrophy severity. Stages III and IV represent patients with an extensive condition.

Table 2 The OLGIM system (Operative Link on Gastric Intestinal Metaplasia)

		Corpus			
	Intestinal metaplasia score	**No intestinal metaplasia (Score 0)**	**Mild intestinal metaplasia (Score 1)**	**Moderate intestinal metaplasia (Score 2)**	**Severe intestinal metaplasia (Score 3)**
Antrum *(including incisura angularis)*	**No intestinal metaplasia (score 0)**	**Stage 0**	**Stage I**	**Stage II**	**Stage II**
	Mild intestinal metaplasia (score 1)	**Stage I**	**Stage I**	**Stage II**	**Stage III**
	Moderate intestinal metaplasia (score 2)	**Stage II**	**Stage II**	**Stage III**	**Stage IV**
	Severe intestinal metaplasia (score 3)	**Stage III**	**Stage III**	**Stage IV**	**Stage IV**

Legend: The Operative Link on Gastric Intestinal Metaplasia table by combining information on intestinal metaplasia in both the antrum and corpus (Capelle, de Vries et al., 2010). Biopsies from the antrum and corpus should be evaluated for the presence and severity of intestinal metaplasia in separate, providing a 2x2 table and defining five stages of intestinal metaplasia severity. Stages 3 or 4 represent patients with an extensive condition.

Other factors are related to progression of these conditions to invasive cancer but their role in the clinical practice is still questionable and difficult to apply in the clinical practice decisions such as the strain of the *H. pylori*, duration of infection, presence or absence of other environmental risk factors (e.g., poor diet, smoking, salt), host genetic factors, in particular genes that regulate expression of pro inflammatory agents (interleukin 1 β, tumour-necrosis factor) and some innate immunity receptors such as toll-like receptors (TLRs) (Abrams & Wang, 2010; Kuipers, Perez-Perez, Meuwissen, & Blaser, 1995; Machado, Figueiredo et al., 2003; Machado, Pharoah et al., 2001; Pereira, Sousa et al., 2006; Pimentel-Nunes, Afonso et al., 2011; Pimentel-Nunes, Goncalves et al., 2013; Pinto-Correia, Sousa et al., 2006). Familial aggregation of gastric cancer also might have some role in about 10% of cases suggesting that a specific surveillance might be desirable, although this is still not consensual (Marcos-Pinto, Carneiro et al., 2012; Marcos-Pinto, Dinis-Ribeiro et al., 2012).

Endoscopy

Upper digestive endoscopy is considered the ideal procedure for the diagnosis of upper digestive system diseases involving the oesophagus, stomach and duodenum. Its widespread availability, the improved accuracy for most diseases, its relatively minor invasiveness and the possibility of simultaneously performing diagnostic biopsies and/or therapeutic procedures usually makes it the first choice for the study of upper digestive diseases (Hirota, Zuckerman et al., 2006). It is usually the first exam performed for the diagnosis of gastric premalignant conditions in patients with gastric complaints but its cost precludes its use as screening tool for gastric cancer in most clinical scenarios.

Even though some efforts at developing screening or diagnostic methodologies to determine the presence and extent of atrophy or intestinal metaplasia have been made, endoscopy alone is said to be inaccurate to determine these changes and the gold standard for diagnosis is histology from biopsies taken during upper endoscopy (Areia, Amaro et al., 2008; Areia, Amaro et al., 2008; Dinis-Ribeiro, da Costa-Pereira et al., 2003).

As Portugal is the Western European country with the highest incidence of gastric cancer it is crucial to have data on prevalence of gastric premalignant conditions (Ferlay, Shin et al., 2010; Hundahl, Phillips, & Menck, 2000). Furthermore, patient acceptance to undergo an endoscopy and the manner in which these exams are performed in terms of associated techniques, use of sedation and complications are mandatory to quantify costs that might be relevant in further economic studies that

consider endoscopy for population screening or follow-up of asymptomatic at-risk patients in Portugal.

Economic studies

Economic studies in medicine are usually designed to compare technologies or clinical strategies by simultaneously addressing their differences in terms of both clinical benefits and the cost involved in achieving those gains (Drummond, Sculper, Torrance, O'Brien, & Stoddart, 2005). The objective is to compare different technologies to achieve the same purpose based on the assumption that financial resources are limited and options have to be made incorporating not only clinical effectiveness but also costs. This concern is mainly driven by politicians and health administrators but should also be adopted by health professionals and the society as well (Drummond, Sculper, Torrance, O'Brien, & Stoddart, 2005).

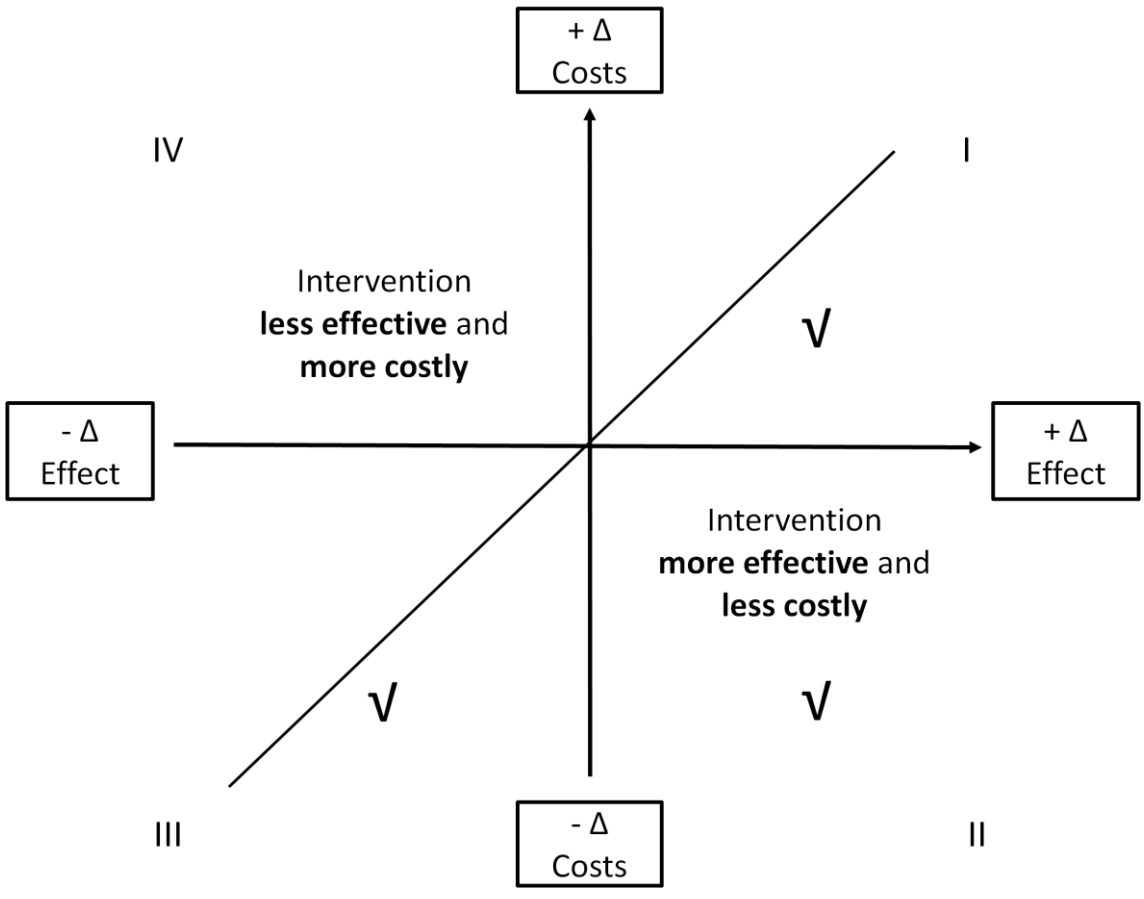
As so, any economic study in the field of medicine is "the comparative analysis of alternative courses of action in terms of both their costs and consequences" and wants to answer simultaneously two questions: which is the best medical option for a specific clinical outcome and what cost is the society willing to pay to obtain that outcome (Drummond, Sculper, Torrance, O'Brien, & Stoddart, 2005).

They can consider the comparators similar in terms of clinical benefits and just address the cost problem (cost-analysis or cost-minimization analysis) or consider the

comparators with different clinical benefits and then compare the different costs involved (cost-effective analysis). When the clinical benefits, for instance life-years saved (LYS), are adjusted to utilities in terms of quality of life (QALY-quality adjusted life years) the studies are called cost-utility analyses and, when the clinical benefit is transformed into a monetary value the studies are called cost-benefit analyses.

The representation of the simultaneous costs and effects of a clinical option can be plotted in a cost-effectiveness plane that will have four quadrants and the willingness to pay frontier defined by the society is represented by a line that crosses the centre of the axis and runs through quadrants I and III as shown in the **figure 3**:

Figure 3 Cost-effectiveness plane



Legend: The cost-effectiveness plane is a simultaneous representation of the difference between two strategies in terms of both costs and effects (Drummond, Sculper, Torrance, O'Brien, & Stoddart, 2005). Costs and effects cross in zero and while the difference in costs changes from negative to positive from bottom to top, the difference in effects changes from negative to positive from left to right, providing four quadrants named by the corresponding Roman numbers I to IV. The willingness to pay frontier defined by the society is represented by a line that crosses the centre of the axis and runs through quadrants I and III. Cost-effective strategies are placed in quadrants I and III below the willingness to pay frontier or in quadrant II. Δ- Difference between strategies in terms of costs or effects. √- Cost-effective strategies.

In general, the alternative or option in study when compared with the present clinical practice will imply a higher cost and the difference has to be quantified and compared to the threshold defined by the society. When plotting effects and cost in the cost-effectiveness plane the option in study usually comes on the right upper side (quadrant I) by providing more effects but at a higher expense (Black, 1990).

Cost-effective strategies should be below the willingness to pay threshold, usually in the quadrant I as already mentioned. In very rare situations the new option will provide more effects with a lower cost (quadrant II). Other rare situations might be below the willingness to pay frontier in quadrant III but are discussible to the society as they will provide less effects although at a lower cost than the actual practice.

The primary outcome measure for any economic evaluation is obtained by calculating the ratio between the difference in costs among strategies that are placed in the numerator and the respective difference in effectiveness that will be placed in the

denominator and this is called the incremental cost effectiveness ratio (ICER), as shown in **figure 4** (Drummond, Sculper, Torrance, O'Brien, & Stoddart, 2005):

Figure 4 Incremental Cost Effectiveness Ratio (ICER)

$$ICER = \frac{\text{Cost new alternative} - \text{Cost current practice alternative}}{\text{Effect new alternative} - \text{Effect current practice alternative}}$$

Legend: The Incremental Cost Effectiveness Ratio is the calculation of a ratio among differences in costs between two strategies versus the difference in effects of the same strategies (Drummond, Sculper, Torrance, O'Brien, & Stoddart, 2005). Costs need to be in the same monetary currency and effects in the same clinical unit, like Life Years Saved (LYS) or Quality Adjusted Life Years (QALY). The first option in each part of the equation is the strategy in study (the study hypothesis) and the second option is the usual strategy in clinical practice (the current standard). ICER- Incremental Cost Effectiveness Ratio.

For diseases that develop for several years and that might impair not only survival but also the quality of that life as well, the standard effectiveness used are the years of life adjusted for they quality, namely the quality adjusted life years (QALY) (Weinstein & Stason, 1977), providing a cost-utility study instead of only a cost-effectiveness analysis. In this form of economic evaluation, the focus is on the quality of the health outcome produced and by incorporating the notion of value have a more broad applicability and are more useful to decision makers (Drummond, Sculper, Torrance, O'Brien, & Stoddart, 2005). Guidelines for the reporting of these studies have for many years recommended conducting cost-utility analysis, where the use of clinical benefits

should be adjusted to patient preferences (Russell, Gold, Siegel, Daniels, & Weinstein, 1996; Siegel, Weinstein, Russell, & Gold, 1996; Weinstein, Siegel, Gold, Kamlet, & Russell, 1996).

Thus, utilities in terms of QALYs means that 1 year of live is multiplied by a utility factor between 1 and 0, providing different values for each single year of life depending on the quality of life of that year, resulting in a value that will vary between 1 QALY (one year with perfect quality of life) and 0 (death, by definition). These guidelines also suggest that preferences should be used by adopting population preferences instead of patient-reported values.

Cost-utility analysis has the advantages in relation to cost-effectiveness analysis of using generic measures like QALY that potentiate comparability among studies, is a method to which various disparate outcomes can be combined into a single measure (QALY) and highlights consumer preferences or utilities, being the preferred method according to guidelines (Drummond & Jefferson, 1996). It is also the ideal method to compare cancer treatments as many of these treatments improve longevity and long-term quality of life but decrease quality of life during the treatment process itself (Drummond, Sculper, Torrance, O'Brien, & Stoddart, 2005).

Preferences are an umbrella that describes the overall concept while utilities and values are different types of preferences, according to the following table as described by Drummond and colleagues (Drummond, Sculper, Torrance, O'Brien, & Stoddart, 2005) **(Table 3)**:

Table 3 Preferences definitions and type of methods

	Question framing	
Response method	**Certainty (values)**	**Uncertainty (utilities)**
	1	*2*
Scaling	Rating scale Category scaling Visual analogue scale Ratio scale	
	3	*4*
Choice	Time trade-off Paired comparison Equivalence Person trade-off	Standard gamble

Legend: Definition of type of preferences according to the options for responding (choice or scaling) and the framing of questions (with certainty or uncertainty), as suggested by Drummond and colleagues (Drummond, Sculper, Torrance, O'Brien, & Stoddart, 2005).

In summary, options in sectors *1* and *3* measure values will those in sector *4* measure utilities. For the calculation of preferences, when using a cardinal measurement, the number must be attached to an outcome that in some sense represents the preference for that outcome in comparison to other and in theory in should be in an interval scale and equal intervals should mean the same difference along the scale (Drummond, Sculper, Torrance, O'Brien, & Stoddart, 2005).

There is no best method and measuring preferences with most of these options are time consuming and complex. As so, in many cases, authors use pre-scored multi-attribute health status classification systems such as the EQ-5D-5L from the EuroQol group as we did for the present thesis (EuroQol, 1990). The preferences scoring for this specific system was done using the time trade-off technique in around 3,000 United

Kingdom adults with the final scores falling in between 0 (death) and 1 (perfect health) (Dolan & Gudex, 1995; EuroQol, 1990; Herdman, Gudex et al., 2011).

Our option on this EQ-5D-5L health status classification system is the result of several advantages: the instrument is established for a long time, is feasible, reliable and valid according to hundreds of published studies, it accommodates attributes that might be relevant for patients with gastric cancer or submitted to treatments for it but at the same time is very general allowing for application and comparison to "healthy" subjects, it is the recommended instrument by the National Institute for Clinical Excellence, it is not very time consuming, is easily applicable even by less instructed patients and finally is available in Portuguese language and was already used in Portuguese gastric cancer patients in the past allowing for comparison of results (Drummond, Sculper, Torrance, O'Brien, & Stoddart, 2005; EuroQol, 1990; Ravasco, Monteiro-Grillo, & Camilo, 2003).

Although the EQ-5D-*5L* questionnaire still has no population norms published for the Portuguese population, the older but similar EQ-5D-*3L* system had only recently set the preferences for the general population using the time trade-off technique and also developed population norms, unfortunately both only after the development of the present thesis and associated studies (Ferreira, Ferreira, Pereira, & Oppe, 2014, 2014).

Because currently there is no validated method to transform utilities from the EQ-5D-3L to the EQ-5D-5L systems, we used the Spanish EQ-5D-5L utilities. From the available options Spanish utilities are the most similar, providing a Pearson's correlation coefficient of r=0.946 for both EQ-5D-3L population norms (Ferreira, Ferreira, Pereira, & Oppe, 2014).

Data from several authors suggests that independently of the pre-scored multi-attribute health status classification system used, health preferences measurements does not vary significantly as a function of demographic variables, including race, income, gender, population or country (Kaplan, 1994; Kaplan & Anderson, 1988; Wang, Furlong, Feeny, Torrance, & Barr, 2002). Also, some authors argue that utility-weighted QALY is a good approximation of utilities in most situations and a good basic definition of what is trying to be achieve in health care (Culyer & Wagstaff, 1993; Garber & Phelps, 1997).

The willingness to pay frontier most widely used is 50,000 United States Dollars (USD) per LYS or per QALY and this value will allow for comparability among results of different models (Shillcutt, Walker, Goodman, & Mills, 2009). Other possibility for this controversial point could be the adoption of a threshold of twice the gross national income per capita as suggested by some institutions (Garber & Phelps, 1997; Sachs, 2001; Tan-Torres Edejer, Baltussen et al., 2003). Independently of the choice, the willingness to pay threshold should be further converted to the local currency of the modelled population (WorldBank, 2013). For Portugal, the option for the USD 50,000 would be 36,575 Euros (€) at a 2013 exchange rate and the option based on the gross national income per capita would be quite similar, USD 41,240 or € 30,433 after conversion.

Finally, the analysis of the model has to be contextualized in terms of the perspective used, meaning that the costs that are incorporated might vary depending on the viewpoint adopted. Guidelines propose that the *society* perspective is the best option as it will incorporate all available costs independently of the professional group

affected, including costs related to the patient, relatives, employers, national health system or insurance companies but other options are used as well such as the *health system*, the *payer* or the *patient'* perspectives only. Depending on the perspective, different cost will be incorporated such as the direct medical costs of the alternatives but also the costs of further surveillance appointments or exams, costs in transportation, outpatient support, productivity changes or costs for absenteeism (Caro, Briggs, Siebert, Kuntz, & Force, 2012; Drummond & Jefferson, 1996).

Published economic studies on endoscopic surveillance of patients

Several studies were published so far on the subject of cost-effectiveness for gastric cancer but many of them were conducted from a primary prevention perspective through *H. pylori* eradication (Davies, Crabbe et al., 2002; Leivo, Salomaa et al., 2004; Mason, Axon et al., 2002; Parsonnet, Harris, Hack, & Owens, 1996; Roderick, Davies et al., 2003; Roderick, Davies et al., 2003; Yeh, Kuntz, Ezzati, & Goldie, 2009) and only a few concerned the use of endoscopic techniques to increase detection of early lesions (Dan, So, & Yeoh, 2006; H. Y. Lee, Park, Jun, Choi, & Hahm, 2010; Y. C. Lee, Lin et al., 2007) or to follow-up of premalignant conditions (Dinis-Ribeiro, da Costa-Pereira, Lopes, & Moreira-Dias, 2007; Hassan, Zullo et al., 2010; Yeh, Hur, Kuntz, Ezzati, & Goldie, 2010) **(Table 4)**.

Table 4 Studies on follow-up of individuals with premalignant conditions and lesions

Study (1st author, year)	Intervention (Population)	Result - ICER	Threshold Unit	Conclusion
Dinis-Ribeiro, 2007	Yearly magnification chromoendoscopy + Serum Pepsinogens (Portugal)	1,868 per QALY	50,000 Euros	Follow-up of patients with atrophic chronic gastritis and intestinal metaplasia is cost-effective
Hassan, 2010	Yearly endoscopy (United States)	72,519 per LYS	100,000 USD	Yearly endoscopy is cost-effective in patients with intestinal metaplasia
Yeh, 2010	Endoscopic surveillance every 1, 5 or 10 years (United States)	39,800 per QALY for dysplasia 544,500 per QALY for intestinal metaplasia	50,000 USD	Endoscopic surveillance of intestinal metaplasia is not cost-effective

Legend: ICER- Incremental Cost Effectiveness Ratio, QALY- Quality Adjusted Life Years, LYS- Life Years Saved, USD- United States Dollars.

Main research question

In light of this, our thesis main research question was to determine the cost-utility of endoscopic surveillance of patients with extensive gastric premalignant conditions in Portugal.

In order to answer this question we performed an economic analysis on the secondary prevention of gastric adenocarcinoma by endoscopic surveillance of patients at high risk of progressing because of extensive atrophy lesions or intestinal metaplasia. The study was designed for the Portuguese population because Portugal has the highest incidence of the disease in Western Europe, the model chosen was a cost-utility Markov model using a societal perspective and the main option was set for a 3-yearly surveillance schedule according to guidelines suggestion.

Chapter III - Aims

The aim of our first study was to conduct a systematic review of studies on cost-effectiveness of upper digestive endoscopy, to obtain the state-of-the-art on economic studies for gastric cancer screening and surveillance of premalignant conditions or lesions. A systematic review of the published literature was undertaken, irrespective of the technology used, type of cost study or clinical scenario, to address in the published literature what was the reported cost-effectiveness of strategies for gastric cancer screening and surveillance of premalignant conditions or lesions versus taking no action.

The aim of our second study was to conduct a systematic review and meta-analysis of studies reporting premalignant conditions (atrophy or intestinal metaplasia) detected by upper digestive endoscopy in both screening and surveillance settings, from a sensitive search in several databases, to assess the global prevalence of gastric premalignant conditions in an aggregated manner by performing a meta-analysis of results and their relation with the gastric cancer incidence of the studied population; secondary objectives were to study the differences in prevalence concerning the methods of assessment, gender, age and *H. pylori* infection.

The aim of our third study was to conduct a cross-sectional study to obtain health utilities from the Portuguese population that would include patients without gastric lesions and also with all sorts of upper gastrointestinal diseases, including patients with all ranges of gastric premalignant conditions and patients with gastric cancer submitted to all available treatments namely endoscopic, surgery, chemotherapy,

radiotherapy or just best supportive care. The pre-scored multi-attribute health status classification system used was the Portuguese version of the EQ-5D-5L questionnaire and the reference test for the diagnosis was the gastroenterologist diagnosis, including the histopathology result when applicable.

Finally, the aim of our forth study and also the final aim of this thesis were to determine the cost-utility of performing a 3 yearly endoscopic surveillance of high risk patients with extensive premalignant conditions versus no surveillance for the Portuguese population, an intermediate incidence population for gastric cancer.

Chapter IV - Publications

Screening for Gastric Cancer and Surveillance of Premalignant Lesions:

a Systematic Review of Cost-Effectiveness Studies

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Screening for Gastric Cancer and Surveillance of Premalignant Lesions: a Systematic Review of Cost-Effectiveness Studies

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Keywords
Atrophic gastritis, costs and benefits , cost-effectiveness , early detection of cancer, gastric cancer, gastric neoplasm, gastrointestinal endoscopy, *Helicobacter pylori* , intestinal metaplasia, Review, stomach neoplasm.

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Abstract

Background: Cost-effectiveness studies are highly dependent on the models, settings, and variables used and should be based on systematic reviews. We systematically reviewed cost-effectiveness studies that address screening for gastric cancer and/or surveillance of precancerous conditions and lesions.

Materials and Methods: A systematic review of cost-effectiveness studies was performed by conducting a sensitive search in seven databases (PubMed, Scopus, Web of Science, Current Contents Connect, Centre for Reviews and Dissemination, Academic Search Complete, and CINAHL Plus), independently evaluated by two investigators. Articles were evaluated for type of study, perspective, model, intervention, incremental cost-effectiveness ratio, clinical or cost variables, and quality, according to published guidelines.

Results: From 2395 abstracts, 23 articles were included: 19 concerning population screening and 4 on following up premalignant lesions. Studies on *Helicobacter pylori* screening concluded that serology was cost-effective, depending on cancer incidence and endoscopy cost (incremental cost-effectiveness ratio: 6264–25,881), and eradication after endoscopic resection was also cost-effective (dominant) based on one study. Studies on imaging screening concluded that endoscopy was more cost-effective than no screening (incremental cost-effectiveness ratio: 3376–26,836). Articles on follow-up of premalignant lesions reported conflicting results (incremental cost-effectiveness ratio: 1868–72,519 for intestinal metaplasia; 18,600–39,800 for dysplasia). Quality assessment revealed a unanimous lack of a detailed systematic review and fulfillment of a median number of 23 items (20–26) of 35 possible ones.

Conclusions: The available evidence shows that *Helicobacter pylori* serology or endoscopic population screening is cost-effective, while endoscopic surveillance of premalignant gastric lesions presents conflicting results. Better implementation of published guidelines and accomplishment of systematic detailed reviews are needed.

Gastric adenocarcinoma represents a health problem worldwide due to its high incidence and mortality rates. It is the fourth most common malignancy and the second leading cause of cancer death [1]. Its prognosis is highly dependent on the stage at diagnosis, usually an advanced stage, requiring demanding treatments and costs [2]. Although it is a worldwide problem, different national prevalence rates have led to different options; in Japan, there is universal screening of the population using fluoroscopy, followed by conventional upper digestive endoscopy with biopsies for the positive results, while in most other developed countries, the low incidence rate makes screening not cost-effective [3,4].

Economic studies in medicine are usually designed to compare technologies or clinical strategies by simultaneously addressing their differences in terms of both

clinical benefits and the cost involved in achieving those gains. They can consider the comparators similar in terms of clinical benefits and just address the cost problem (cost analysis or cost-minimization analysis) or consider the comparators with different clinical benefits and then compare the different costs involved (cost-effective analysis). Where the clinical benefits, for instance life-years saved (LYS), are adjusted to utilities in terms of quality of life (QALY – quality-adjusted life-years), the studies are called cost-utility analyses, and when the clinical benefit is transformed into a monetary value, the studies are called cost-benefit analyses.

Upper digestive endoscopy is considered the ideal procedure for the diagnosis of upper digestive system diseases involving the esophagus, stomach, and duodenum. Its widespread availability, the improved accuracy for most diseases, its relatively minor invasiveness, and the possibility of simultaneously performing diagnostic biopsies and/or therapeutic procedures usually make it the first choice for the study of upper digestive diseases [3]. It is usually the first examination performed for the diagnosis of premalignant gastric lesions in patients with gastric complaints, but its cost precludes its use as screening tool for gastric cancer in most clinical scenarios.

For gastric cancer prevention, several options can be adopted, namely *Helicobacter pylori* screening and treatment of positive cases to prevent the biologic evolution from normal gastric mucosa to premalignant lesions and to invasive cancer; endoscopic screening for early gastric cancer detection in earlier stages with more favorable survival; or endoscopic surveillance of patients with premalignant lesions to allow detection and removal of dysplastic lesions just before they progress to an invasive state [5].

This gastric cancer prevention problem can be best tackled by conducting cost-effectiveness studies where, for each circumstance specified, both the costs involved and the clinical benefits obtained can be estimated for the technologies compared. Several studies have been published in the last two decades using this approach for gastric cancer, but to the best of our knowledge, no systematic review has yet been published that enables comparison of the several strategies, scenarios, and technologies studied, the results obtained, and identification of the relevant variables or limitations of these studies. Also, as each cost-effectiveness study should be based on a broad review of the available literature, the publication of a systematic review could help the design of future studies by providing the best available evidence at a given point in time.

Thus, the aim of our study was to obtain the state of the art on cost-effectiveness studies for gastric cancer screening and surveillance of premalignant conditions or lesions. A systematic review of the published literature was undertaken, irrespective of the technology used, type of cost study, or clinical scenario, to address in the published literature what is the reported cost-effectiveness of strategies for gastric cancer screening and surveillance of premalignant conditions or lesions versus taking no action.

Methods

Type of Study and Selection of Manuscripts

A systematic review of cost-effectiveness studies was performed by conducting a sensitive search in several databases. The protocol terms used to perform the search were chosen to obtain cost-effectiveness studies for gastric cancer screening or surveillance of premalignant conditions or lesions, but intentionally excluding cancer treatment. Eight terms were used for the type of study: cost benefit OR cost effectiveness OR cost utility OR cost analysis OR Markov model OR cost OR costs OR economic; for the study population, we used 3 terms: screening OR endoscopy OR endoscopic, and for the problems addressed, 7 terms were used: stomach neoplasm OR gastric cancer OR *H. pylori* OR atrophy OR gastritis OR intestinal metaplasia OR dysplasia.

The search was conducted on July 28, 2012, in these seven databases: PubMed, Scopus, Web of Science, Current Contents Connect, Centre for Reviews and Dissemination, Academic Search Complete, and CINAHL Plus. The following options were used to define the type of entry in each database: "Title/abstract" in PubMed, "Title/abstract/keywords" in Scopus, "Topic" in Web of Knowledge, "Title" in Centre for Reviews and Dissemination, and "Abstract" in both Academic Search Complete and CINAHL Plus. No filters or restrictions, that is, language, type of study, year of publication, or publication status, were used.

An example of a full electronic search strategy for the PubMed search would be: "(cost benefit [Title/abstract] OR cost effectiveness [Title/abstract] OR cost utility [Title/abstract] OR cost analysis [Title/abstract] OR Markov model [Title/abstract] OR cost [Title/abstract] OR costs [Title/abstract] OR economic [Title/abstract]) AND (screening [Title/abstract] OR endoscopy [Title/abstract] OR endoscopic [Title/abstract]) AND (stomach neoplasm [Title/abstract] OR gastric cancer [Title/abstract] OR Helicobacter pylori [Title/abstract] OR atrophy [Title/abstract] OR gastritis [Title/abstract] OR intestinal metaplasia [Title/abstract] OR dysplasia [Title/abstract])."

All article titles and abstracts retrieved from the query in the databases were independently evaluated by two investigators with a previously defined broad

inclusion criterion (gastric cancer as topic) and excluding all other nonrelevant articles (nonmedical, nongastroenterological, nongastric, or gastric other than cancer articles). The remaining studies' titles, abstracts, and full texts were assessed to identify cost-analysis studies, excluding noncost studies or cost studies on other issues like dyspepsia or ulcers). Finally, all the remaining articles were reviewed in full to confirm that they were specific to the issue in question. To search for any missing article not detected so far, all included citations were cross-referenced, and references from review articles were also examined.

In all these steps, concordance was measured between observers by proportion of agreement and kappa statistics, consensus meetings were held to resolve disagreements, and a record of reasons for exclusion was kept.

Data Extraction

For each study retrieved, the final full report was assessed for a list of predefined items such as: type of study, type of model used and year of its conception, intervention in study and comparator used, population involved, time frame, and perspective used. Also, we looked in the results for the effectiveness estimate used (LYS, QALY), incremental cost-effectiveness ratio values (ICER), threshold considered and adjustments for currency [United States dollars (USD) or others] and/or inflation, number of clinical and cost variables used, and type of sensitivity analysis performed. Finally, conclusions and relevant variables in sensitivity analyses were identified.

Risk of bias of individual studies was assessed by looking for limitations according to published guidelines, and all articles were evaluated for the fulfilling or not of each of the 35 items recommended [6]. Results are presented in accordance with the PRISMA statement recommendations and reported as mean and standard deviation, medians and interquartile range or percentages, and 95% confidence intervals. No data combining was performed due to the lack of a statistical methodology to aggregate results of these types of studies [7].

Results

Description of the Studies

A search was performed to identify all relevant articles and 2673 articles were returned (Fig. 1). From that list, after the exclusion of duplicates, 2395 articles were independently evaluated by two authors to identify those related only to gastric cancer and providing a

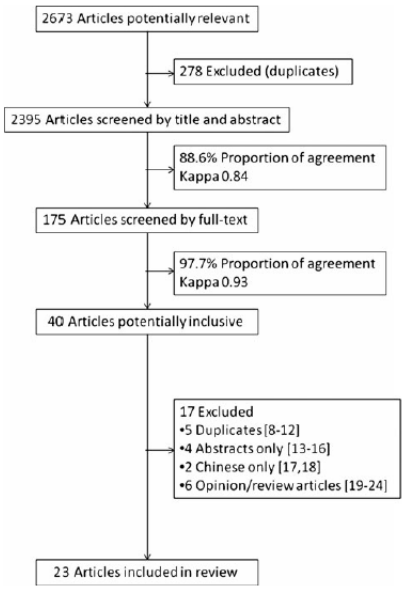

Figure 1 Flowchart of article evaluation for inclusion in the study.

proportion of agreement of 88.6% and a kappa correlation coefficient of 0.84. The other 175 articles were again assessed independently by title, abstract, and full text as needed, to identify only cost-effectiveness studies concerning gastric cancer screening or detection, and 40 articles were selected, with a proportion of agreement of 97.7% and a kappa correlation coefficient of 0.93. After a consensus meeting, 17 articles were excluded: five for duplication [8–12], four for presentation in abstract form only [13–16], two for being written in Chinese only [17,18], and six opinion/review articles [19–24]. The final result returned 23 articles concerning cost analysis in gastric cancer.

Of the 23 articles considered, 19 report on population screening scenarios [25–43], one on *H. pylori* screening after early gastric cancer removal [44], and three on follow-up of populations with premalignant lesions (Table 1) [45–47]. Of those 19 articles on screening options, 12 discussed the various methods for *H. pylori* screening with eradication of positive cases in several populations or subgroups of patients [25–36], while seven studied radiologic or endoscopic methods of screening for early gastric cancer [37–43]. Only one model studied the effect of eradicating *H. pylori* after the endoscopic resection of early gastric cancer [44]. The articles on follow-up of populations with premalignant conditions or lesions studied the endoscopic surveillance of patients with atrophic gastritis, intestinal metaplasia, or dysplasia [45–47].

Table 1 Articles included in the systematic review: main characteristics

Conclusion	Study (1st author, year)	Type of study/ country, year	Intervention	Result (ICER or other)/range	Threshold/unit	Model/ population	Sensitivity analysis	Source of effectiveness	Clinical/cost variables	Relevant variables in sensitivity analysis	Limitations
(a) Studies on *H. pylori* infection screening for gastric cancer prevention											
Screening for *H. pylori* is cost-effective	Parsonnet, 1996 [25]	Cost-effectiveness/ USA, 1984	Screening (serology) and treating *H. pylori*	ICER 25,000 per LYS (4800–152,100)	Unknown US dollars	Markov 50y	One way	LYS	11/3	Cancer reduction efficacy and age at screening	Literature review unclear
	Fendrick, 1999 [26]	Cost-effectiveness/ USA, 1996	Screening (serology) and treating *H. pylori* or Screening, treating and retreating	ICER 6264 per LYS	50,000 US dollars	Markov 40y	One way	LYS	10/5	Cancer reduction efficacy	Literature review unclear
	Harris, 1999 [27]	Cost-effectiveness / USA, 1995	Screening (serology) and treating all or screening and treating only CagA+	ICER 24,300 per LYS (all Hp) ICER 23,900 per LYS (CagA+ Hp)	50,000 US dollars	Markov 50y	One way	LYS	12/3	Gastric cancer prevalence, cancer reduction efficacy, and age at screening	Literature review unclear ICER calculations without cancer treatment costs
	Davies, 2002 [28]	Cost-effectiveness/ UK, 2000	Screening (UBT) and treating *H. pylori*	Cost 368,045 per LYS 352,686–383,404	Unknown UK pounds	Discrete event simulation 50y	Factorial design	LYS	7/8	Gastric cancer prevalence *and H. pylori* prevalence	Literature review unclear No cost-benefit calculation Sensitivity on costs not performed.
	Mason, 2002 [29]	Cost-effectiveness/ UK, unknown	Screening (UBT) and treating *H. pylori*	Dominant to no screening	Unknown UK pounds	Markov 40–49y	One way, two way	LYS	9/5	Gastric cancer prevalence, *H. pylori* prevalence, and Dyspepsia costs	Systematic review not performed
	Roderick, 2003 [30]	Cost-effectiveness/ England and Wales, 2000	Screening (serology) and treating *H. pylori*	CER (not incremental) 5866 per LYS 1858–9023	Unknown UK pounds	Discrete event simulation 20–50y	Factorial design	LYS	10/11	Age at screening, risk of gastric cancer, risk of gastric ulcer, and *H. pylori* prevalence	Literature review unclear. No incremental ratio results.
	Leivo, 2004 [31]	Cost minimization/ Finland, 1999	Screening (serology) and treating *H. pylori*	IC 26 per screening 15–38	Unknown US dollars	Decision analytic tree 5–45y	One way, multiway, probabilistic	Incremental cost per screen	22/21	Age at screening, *H. pylori*-related cancers, *and H. pylori*-related lesions	Systematic review not performed

(Continued)

Table 1 *(Continued)*

Conclusion	Study (1st author, year)	Type of study/ country, year	Intervention	Result (ICER or other)/range	Threshold/unit	Model/ population	Sensitivity analysis	Source of effectiveness	Clinical/cost variables	Relevant variables in sensitivity analysis	Limitations
	Lee, 2007 [32]	Cost-effectiveness/ Taiwan, 2005	Screening (UBT) and treating *H. pylori* or serum pepsinogens and endoscopy	ICER 17,044 per LYS	50,000 US dollars	Markov 30y versus 50y	One way, probabilistic	LYS	19/10	*H. pylori* prevalence, early cancer rate, and age at screening	Systematic review not performed
	Xie, 2008 [33]	Cost utility/ Singapore, 2006	Screening (serology) and treating *H. pylori* or screening (UBT) and treating *H. pylori*	ICER 16,166 per LYS ICER 13,571 per QALY	28,000 US dollars	Markov 35–44y Chinese male	One way	LYS, QALY	15/5	Gastric cancer prevalence, *H. pylori* prevalence, cancer risk reduction, age at screening, and cancer treatment cost	Literature review not detailed Utility valuations not detailed
	Xie, 2008 [34]	Cost utility/ Singapore, 2006	Screening (serology) and treating *H. pylori* or screening (UBT) and treating *H. pylori*	ICER 25,881 (serology) per QALY (5,700–120,000)	50,000 US dollars	Markov 40y Chinese	Probabilistic	LYS, QALY	15/5	Gastric cancer prevalence, *H. pylori* prevalence, and willingness-to-pay	Literature review not detailed Utility valuations not detailed
	Xie, 2009[35]	Cost utility/Canada, 2008	Screening (Stool Ag) or screening (serology) or Screening (UBT)	ICER 29,800 (stool Ag) per QALY	Unknown Canadian dollars	Markov 35y male	One way, probabilistic	QALY	18/5	Gastric cancer prevalence, *H. pylori* prevalence, willingness-to-pay, and cost of screening test	Literature review not detailed Utility valuations not detailed
	Yeh, 2009 [36]	Cost utility/China, 2005	Screening (serology) once and treating *H. pylori* or screening twice and treating *H. pylori* or universal treatment	ICER 1,340 per LYS ICER 1,560 per QALY	1700 Chinese Yuan	Markov 20y	One way, multiway	LYS, QALY	12/6	*H. pylori* prevalence, age at screening, treatment effectiveness, *H. pylori* diagnosis, and treatment cost	Literature review not detailed Utility valuations not detailed Patient time costs only in sensitivity analysis
Studies on *H. pylori* screening after endoscopic removal of gastric cancer											
Treatment of *H. pylori* after endoscopic resection is cost-effective	Shin, 2009 [44]	Cost-effectiveness/ South Korea, 2007	Treating *H. pylori* after endoscopic resection	Dominant (lower costs and more LYS)	20,000 US dollars	Markov 60y after endoscopic resection of early gastric cancer	One-way, three-way	LYS	7/8	Risk of metachronous lesions and cancer treatment cost	Systematic review not performed. Inflation adjustments and US dollar conversions not described

(Continued)

Table 1 *(Continued)*

Conclusion	Study (1st author, year)	Type of study/ country, year	Intervention	Result (ICER or other)/range	Threshold/unit	Model/ population	Sensitivity analysis	Source of effectiveness	Clinical/cost variables	Relevant variables in sensitivity analysis	Limitations
(b) Studies on imaging screening for precancerous lesions or gastric cancer detection											
Indirect X-ray screening is cost-effective	Tsuji, 1991 [37]	Cost-effectiveness/ Japan, 1987	Indirect X-ray	606,300 for male per LYS 1,542,500 for female per LYS	Unknown Yen	Unknown >40y	Not performed	LYS	6/4	Age at screening and cancer incidence	Systematic review not performed. No incremental analysis
	Babazono, 1995 [38]	Cost-effectiveness/ Japan, unknown	Indirect X ray or direct X ray or endoscopy	ICER 6,376 if 70y male per LYS ICER 50,888 if 40y per LYS	Unknown US dollars, Yen	Markov >40y	One-way	LYS	24/10	Age at screening and cancer incidence	Systematic review not performed. Costs from expert opinion
Endoscopic screening is cost-effective	Dan, 2006[39]	Cost utility/ Singapore, 2003	Endoscopy every 2 years	ICER 26,836 per LYS ICER 28,000 per QALY (6,925–66,382)	28,000 US dollars	Markov 50–70y Chinese male	One-way, Two-way	LYS, QALY	6/4	Cancer incidence, age at screening, endoscopy cost, and cancer stage at screening	Literature review unclear Societal perspective not detailed
	Tashiro, 2006 [40]	Cost minimization/ Japan, 2004	Endoscopy or X-ray	Cost 1.998.000 for endoscopy	Unknown Yen	Unknown >40y	Not performed	Cost per case detected	2/3	Endoscopy cost and endoscopic availability	Systematic review not performed. Absence of screening comparator No effectiveness calculation
	Lee, 2010 [41]	Cost minimization/ South Korea, 2008	X-ray every 2 years or endoscopy every 2 years	16,900 per endoscopy (6,925–66,382)	Unknown US dollars	Unknown 40y	Not performed	Cost per case detected	4/5	Cost of screening technology	Systematic review not performed No effectiveness calculation
	Gupta, 2011 [42]	Cost utility/USA, 2009	Endoscopy + Barrett's surveillance or endoscopy	ICER 95,559 per QALY	100,000 US dollars	Markov 50y undergoing colonoscopy	One-way, Multi-way	QALY	19/10	Endoscopy cost and quality of life for Barrett's esophagus patients	Literature review not detailed Utility valuations not detailed.
	Zhou, 2011 [43]	Cost utility /China, unknown	Serum pepsinogens + Endoscopy	5,249 per case; 459 per QALY	Unknown Chinese Yuan	Case-control study 35y High-risk population	Not performed	Cost per case, QALY	4/3	Endoscopy cost and cancer treatment cost	Systematic review not performed Utility valuations not detailed. No incremental calculation
(c) Studies on follow-up of individuals with premalignant conditions and lesions											
Follow-up of patients with atrophic chronic gastritis and intestinal metaplasia is cost-effective	Dinis-Ribeiro, 2007 [45]	Cost utility/Portugal, unknown	Yearly magnification chromoendoscopy + Serum Pepsinogens	ICER 1,868 per QALY (1,257–3,078)	Unknown Euros	Markov cohort with premalignant lesions	One way	QALY	3/6	Quality of life after surgery and chemotherapy cost	Literature review unclear Costs and benefits combining unclear Discount not performed
Yearly endoscopy is cost-effective in patients with intestinal metaplasia	Hassan, 2010 [46]	Cost-effectiveness/ USA, 2008	Yearly endoscopy	ICER 72,519 per LYS (54,843–98,853)	100,000 US dollars	Markov 60y	Two way, probabilistic	LYS	7/2	Cancer incidence reduction, cancer downstaging, and age at surveillance	Literature review unclear Simplistic model

(Continued)

Table 1 *(Continued)*

Conclusion	Study (1st author, year)	Type of study/ country, year	Intervention	Result (ICER or other)/range	Threshold/unit	Model/ population	Sensitivity analysis	Source of effectiveness	Clinical/cost variables	Relevant variables in sensitivity analysis	Limitations
Endoscopic surveillance of gastric dysplasia every 1 to 5y with endoscopic resection as treatment is cost-effective	Yeh, 2010 [47]	Cost utility/USA, 2007	Endoscopic surveillance every 1, 5 or 10 years	ICER 39,800 per QALY if 1y ICER 20,900 per QALY if 5y ICER 18,600 per QALY if 10y	50,000 US dollars	Markov 50 y male with gastric premalignant lesions	One way, probabilistic	QALY	25/10	Surgical risks, proportion of resection completion, type of premalignant lesion, and post-treatment surveillance	Literature review unclear Utility valuations not detailed

ICER, incremental cost-effectiveness ratio; LYS, life-years saved; QALY, quality-adjusted life-years; US, United States; UK, United Kingdom; UBT, urea breath test; year in study stands for year of publication; year in type of study stands for year considered for cost in the model.

Cost-effectiveness analysis was the most common approach (52%), with only 35% adopting a cost-utility analysis and 13% cost-minimization results only, without effectiveness estimates. The point of view taken was almost unanimously the health service perspective, and only three articles used a societal one [32,36,47]. Most studies used LYS and/or QALY as effectiveness estimates, but some studies limited their results on costs and so did not perform a full economic evaluation. All studies reported the currency, but less than half (43%) failed to clearly state the threshold used in the study, adjusting the results obtained to an undefined hypothetical value that sometimes ranged between 50,000 and 100,000 USD. The median number of variables used was 10 [6–18] for the clinical estimates and 5 [4–10] for cost estimates.

Unfortunately, there is still no statistical method to aggregate the results of studies of this type, and one may never become available. However, considering the results, all the articles were very clear when reporting their final conclusion: all studies on screening for *H. pylori* concluded that it was cost-effective, usually by serology (the exception was a study in Canada that concluded that stool antigen testing was more cost-effective) [35], with adjustments for the age of screening depending on the population studied; studies on population imaging screening concluded that endoscopy was more cost-effective than no screening, or better than X-ray, and that X-ray was more cost-effective than no screening [37–43]. Articles on the follow-up of patients with premalignant conditions or lesions reported conflicting results, with some studies concluding that endoscopic surveillance was cost-effective for patients with intestinal metaplasia lesions [45,46], while others concluded that it was cost-effective only in patients with dysplasia [47].

In the sensitivity analysis, most articles were also clear in pointing out the clinical or cost variables that might alter the final result, with some variables being very consistent among most studies: *H. pylori* and gastric cancer incidences (that relates to age, gender, and population), age at screening, the estimated cancer reduction achieved by the option studied (screening, eradication, or endoscopic detection of early gastric lesions), and cost of endoscopy and/or cancer treatment (just chemotherapy or overall).

Quality Assessment

Concerning quality, all articles were evaluated according to the suggestions in the guidelines published on the reporting of economic studies (Fig. 2) [6]. The

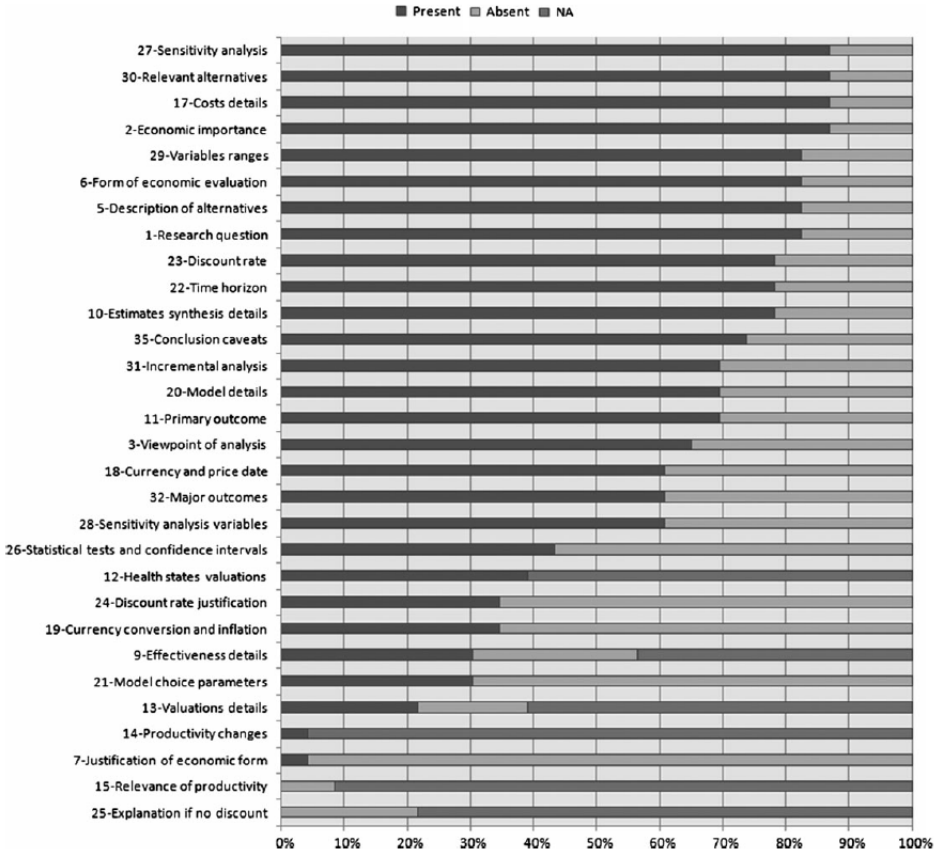

Figure 2 Fulfillment of items of the articles according to guidelines. Item title and number according to the original manuscript by Drummond et al. (1996) [6]. Present: the item information was reported in the article; Absent: the item information was not found in the article. NA: the item is not applicable in the article.

median number of items fulfilled was 23 [20–26] of 35 items possible, and although they are not of the same importance in terms of quality of the article, only eight items were reported in more that 80% of the articles, while 10 items did not achieve at least a 40% presence in all articles. More importantly, four items that are fundamental when assessing this kind of article were present in only around 60% of the studies, in particular the incremental analysis and major outcomes results (items 31 and 32), the price dates used (item 18), and the model details (item 20). Also, although not an item of the guidelines suggestions but very important to the Oxford stratification of the available evidence, the lack of a systematic detailed review of the available literature was a unanimous limitation of the studies, indicating the pertinence of the present review [48].

Studies on *H. pylori* Infection Screening for Gastric Cancer Prevention

Concerning studies on screening for *H. pylori*, 12 compared universal unselected population screening and eradication of positive cases versus no screening and concluded that it was cost-effective. Most studies used serology screening in the model, but two compared urea breath test versus nothing [28,29] and reached the same conclusion; when the two screening alternatives were compared, serology screening was more cost-effective than the urea breath test [33–35]. The only study that modeled the stool antigen method concluded that it was more cost-effective than the other two alternatives [35]. Studies presented ICER values per LYS or per QALY ranging from 6264 to 25,881, well below the most common 50,000 USD threshold, independently of

the study setting being a high-risk (i.e., far East) or low-risk (i.e., North America or Europe) country. Others adjusted the threshold for the average gross national product and reached the same conclusion [34,36]. When addressing the question of what was the best time to start screening, most authors reached the same conclusion: the later the better! Several authors concluded that screening at ages above 50 years old had always lower ICER values than screening options starting before the age of 50 [25,37,38]. Even for the authors who only evaluated younger ages below 50, the conclusion remained with increasing ICER values as the screening starting age drops [27,30,31,33]. The only exceptions were two studies with the opposite conclusion, probably related to the assumptions made on the declining gastric cancer incidence reduction related to age [32,36] (Table 1a).

Studies on *H. pylori* Screening After Endoscopic Removal of Gastric Cancer

Only one study addressed the problem of *H. pylori* screening after early gastric cancer removal by endoscopy, and it concluded that the strategy of *H. pylori* screening and eradication of positive cases were dominant versus no action, as it offered lower associated costs and provided more LYS, even for an adopted threshold of only 20,000 [44]. Results were sensitive only to cancer treatment costs and risk of metachronous lesions (Table 1a).

Studies on Imaging Screening for Precancerous Lesions or Gastric Cancer Detection

For studies on population imaging screening, three studies comparing endoscopy versus no action agreed that endoscopy was more cost-effective, with ICER values below the various adopted thresholds [39,42,43], while two studies comparing endoscopy versus X-ray concluded that endoscopy was more cost-effective, although they used different monetary units [40,41]. All these studies come from high-risk populations of the Far East except one from the United States that used a selected population of patients undergoing Barrett's surveillance [42]. The two studies that compared X-ray versus no action also concluded that screening was more cost-effective than no screening, again using different monetary units [37,38]. When conducting sensitivity analysis with different schedules for endoscopic screening, Dan and colleagues and Lee and colleagues did not found any statistical difference between choosing endoscopic examinations every 2 versus 3 years or every 1 versus 5 years, respectively [32,39] (Table 1b).

Studies on Follow-up of Individuals with Premalignant Conditions and Lesions

Only three articles modeled the endoscopic follow-up of patients with premalignant gastric conditions or lesions, and their conflicting results might be explained by different progression rates assumptions. Two studies that addressed the surveillance of patients with intestinal metaplasia concluded that endoscopic follow-up was cost-effective, with ICER values between 1868 and 72,519, but below the adopted threshold [45,46], while another study addressing patients with intestinal metaplasia or dysplasia concluded that only in patients with dysplasia was endoscopic surveillance cost-effective, with ICER values ranging from 18,600 to 39,800 depending on the endoscopic intervals, all below the 50,000 threshold [47]. These conflicting results might arise from very different estimates of the yearly rates for progression of conditions: 0.0–1.2% from dysplasia to invasive cancer in the study of Yeh et al. [47]; 0.18% from intestinal metaplasia to cancer in Hassan and colleagues [46]; and 12.8%–56.0% from intestinal metaplasia to dysplasia in the study by Dinis-Ribeiro and colleagues [45]. Also, differences might arise from the cost estimates included in the models (cost per endoscopy of 871 USD versus 358 USD in the studies by Yeh et al. [47] and Hassan et al. [46], respectively, the assumption or not of lesions regression, and also the fact that in some studies, undiscounted costs or benefits were used [45], impeding a clear comparison of ICER values among studies. Finally, estimates on cancer incidence or mortality reduction were not clear (but different 5-year stage-specific disease mortality was used among the three studies), and while Hassan et al. used LYS as outcome, Yeh and colleagues and Dinis-Ribeiro and colleagues used QALY. Results were most sensitive to costs and quality of life after chemotherapy and surgery (Table 1c).

Discussion

Gastric adenocarcinoma is a worldwide problem, but different national prevalence rates lead to different approaches to solve it. Cost-analysis studies are conceived to compare technologies or clinical strategies by simultaneously addressing their differences in clinical benefits and costs and are a good choice to evaluate the most suitable clinical option for a given population, according to its characteristics and financial conditions.

Several cost-effectiveness studies have been published in the last two decades on gastric cancer, but to the best of our knowledge, no systematic review has yet been published on the topic. Also, as each cost-effectiveness study should be based on a broad review

of the available literature, the publication of such a systematic review could help the design of future studies by providing the best available evidence at a given point in time.

We think that this systematic review has accomplished that objective and can provide clinicians interested in this kind of clinical approach with the best available evidence so far. The robustness of our review stems from the systematic search performed in several databases, the independent evaluation of the articles by two reviewers and the methodical extraction of results, guidelines fulfillment, general conclusions, and limitations of the studies.

The general conclusion on the best approach to improve the detection of early gastric cancer was that screening for *H. pylori* and treating the positive cases were always cost-effective, just needing to adjust the age at screening, which was relevant in the sensitivity analysis. According to most of the authors, it was better to screen above the age of 50 than before, and all but one study reported that serology was the best method to perform such screening. The only article on patient management after endoscopic resection of early gastric cancer favors the eradication of *H. pylori* in positive patients [44]. Interestingly, although using very different models, perspectives, assumptions, and data in their studies, the conclusion on the benefit of *H. pylori* eradication was unanimous. Sensitivity analysis on gastric cancer prevalence showed that even for populations with prevalence rates as low as 4.2 per 100,000, the option of serology screening was cost-effective [25,27,34].

However, these results are in contradiction with the only randomized controlled trial published so far by Wong and colleagues in 2004, testing the effect of *H. pylori* eradication versus placebo in the prevention of gastric cancer [49]. Wong and colleagues found that *H. pylori* eradication was effective only in the subgroup of patients still without premalignant lesions, in a very early stage of the *H. pylori* infection. Possible explanations for this discrepancy might be the fact that the study was carried out in a high-risk population and the result was found only in subgroup analysis, not confirmed by any other randomized study designed for this specific population, while costs may be lower with targeted screening, the effectiveness may not be warranted if the proportion of individuals at age 50 without precancerous lesions who would benefit from treatment is small and also individuals without premalignant lesions at age 50 might not develop gastric cancer within their lifetime (these individuals may be at elevated risk for gastric cancer, but many would die from competing causes before developing invasive cancer). As such, *H. pylori* treatment may not reduce gastric cancer incidence among individuals 50 years and older.

With respect to endoscopy, studies concluded it was more cost-effective than no screening, but depended mainly on its cost and with only one study conducted in a low-risk population [39,40,42,43]. When different schedule options for endoscopic screening were analyzed, the ICER results would vary, but still remain below the 50,000 USD threshold. These results are in accordance with a recent endoscopic screening study from a high-risk population in Korea that concluded that endoscopic intervals of 3 years or below showed similar protective benefits in relation to the detection of an advanced gastric cancer stage disease [50].

The available evidence on endoscopic follow-up of patients with premalignant lesions is contradictory and limited to three studies. One article claims that the surveillance of patients with atrophic gastritis or intestinal metaplasia is cost-effective [45], while another agrees with that but at a threshold value that is twice the one usually accepted in most economic analyses [46]. A third study concludes that endoscopy is cost-effective only in patients with dysplasia [47]. These conflicting results seem to be related to different assumptions on the progression or regression of lesions and different estimates for the 5-year stage-specific mortality. Clearly, this area of endoscopic surveillance is requiring more economic studies, models, and better scientific evidence as most of the published literature reports on clinical follow-up without considering the cost-effectiveness point of view.

According to the Oxford stratification of the available evidence [48], rating a study as grade 1 or 2 depends mainly on the quality of the systematic review, and we would conclude that not a single study claiming to have performed such systematic review was able to detail its approach. As such, all studies are considered by us to be grade 2, at best. With this assumption, we may then conclude that any suggestion from these studies will not exceed a level of evidence of 2 or a grade of recommendation of B.

When addressing the problems of cost-effectiveness studies already identified by the consensus statements published in 1996, which were intended to improve comparability and quality of studies, we conclude that even after all these years, the problems remain, similar to other medical fields [51–54]: although it was found in only one study, we continue to have models that do not use the "no action" option in the reference case [40], only three articles adopted the societal perspective recommended by the guidelines [32,36,47], only one-third of the studies used both length of time (LYS) and quality of that time (QALY) as effectiveness estimates,

and most studies used patient preferences instead of the recommended community preferences [33–36,39,42,43,45,47].

With this first systematic review on this topic, we are able to offer some recommendations to improve the quality and comparability of future models and studies: when comparing clinical options, the model should always have a "no action" alternative; the societal perspective should be added to the more generally used health service one, as it represents the public rather than a particular group interest, and only a little extra expenditure would be needed to include it in the model; all studies should include both cost-effectiveness estimates, such as LYS, and also cost-utility analysis with QALY, to include patient preferences in clinical gains and present both outcomes, again to improve comparability; finally, authors need to detail the systematic review they claim to have performed to attain a higher level in the evidence scales. For this last item, we think we have provided an example that can be used and improved by authors. If all these methodological steps are adopted, quality will certainly improve and eventually lead to a statistical analytic tool to aggregate results, as is already available to other studies such as randomized controlled trials.

Our study also presents some limitations that need to be noted. The systematic review could have been improved by refining the query used, searching in other databases, making personal contact with authors, searching in gray literature, and manual searching medical journals. But not a single new article was detected either in the references of the articles included or in the review articles consulted. In addition, two Chinese articles were detected but excluded because there was no reliable scientific translation available. Another limitation arises from the quantification of article quality by the fulfillment of guideline items when they quite certainly do not have the same importance in terms of quality, but without an alternative, this seems to us to be a valid method. Finally, due to the lack of a statistical method to aggregate different cost-effectiveness results, conclusions can only be labeled in general, according to levels of evidence but without a single final result.

In conclusion, to the best of our knowledge, this study presents the first systematic review ever published on cost-effectiveness studies on gastric cancer screening, premalignant conditions, or lesion surveillance. The available evidence shows that *H. pylori* serology population screening with treatment of positive cases is cost-effective, with adjustments to the screening age according to *H. pylori* prevalence or even after early gastric cancer endoscopic resection. Endoscopy is also a cost-effective population screening option, depending on the gastric cancer incidence and cost of the endoscopy. At the moment, conflicting results do not allow agreement on the endoscopic surveillance of gastric premalignant conditions or lesions.

More studies are needed in this field, and better implementation of published guidelines is desirable. We hope this study has provided the best evidence so far in this area and believe that it might be in the best interest of clinicians to investigate this issue further.

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Prevalence of Gastric Precancerous Conditions:

A Systematic Review and Meta-analysis

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Prevalence of gastric precancerous conditions: a systematic review and meta-analysis

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Several reports of estimates for precancerous conditions for gastric adenocarcinoma can be found in the current literature. Our aim was to systematically review and estimate the prevalence of gastric precancerous conditions. Four databases (PubMed, Scopus, Web of Knowledge and EBSCO Academic Search Complete) were searched for original manuscripts addressing the presence of chronic atrophic gastritis (CAG) or intestinal metaplasia (IM). Subgroup analysis was carried out on methods of diagnosis, type of population, incidence of gastric cancer, sex, *Helicobacter pylori* status, age and extent of conditions. Overall, 107 studies were included. The worldwide prevalence of CAG in the general population was 33% (95% confidence interval: 26–41%) when considering biopsies ($n=20\,912$) and 24% (19–29%) if serology ($n=51\,886$) was used, whereas IM was found in 25% (19–30%) ($n=30\,960$). Estimates for CAG were higher in countries with a high incidence of gastric cancer (42 vs. 23%), men (32 vs. 28%), *H. pylori* positive (46 vs. 17%) and if aged 40 years or older (48 vs. 22%). The prevalence of extensive conditions was 16% (12–20%) for CAG and 13% (9.0–17%) for IM. When comparing countries with high versus low to moderate incidence of gastric cancer, significant differences were achieved for CAG: 27% (12–36%) versus 7.3% (5.6–9.0%). Worldwide, one-third and one-fourth of individuals may harbour CAG and IM, respectively. In countries with a high incidence of gastric cancer, the prevalence of extensive conditions may increase up to 27% and these patients represent a high-risk population to whom endoscopic surveillance should be offered according to recent guidelines. *Eur J Gastroenterol Hepatol* 26:378–387

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Keywords: atrophic gastritis, gastric cancer, gastric neoplasm, gastrointestinal endoscopy, *Helicobacter pylori*, intestinal metaplasia, meta-analysis, pepsinogens, review, stomach neoplasm

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Introduction

Gastric cancer is the fourth most common cancer and the second leading cause of cancer death worldwide. Its geographical incidence varies considerably, being particularly marked in Eastern Asia, Central and Eastern Europe, and South and Central America, and although a decrease in its incidence is being observed, its burden is still unacceptably high [1].

The intestinal subtype of this cancer is known to be preceded by a cascade of precancerous conditions and lesions, namely chronic atrophic gastritis (CAG), intestinal metaplasia (IM) and gastric dysplasia [2,3], and several different classifications exist for their histological classification [4–7]. On the basis of the assumption that chronic gastritis starts in the antrum and then spreads to the corpus in an upward manner, so that conditions of the corpus are more extensive and related to more advanced stages, it has been suggested to discriminate this phenotype at an increased risk of progression to dysplasia and invasive cancer [8].

Helicobacter pylori infection was first considered a class I carcinogen at the International Agency on Research for Cancer in 1994 and is a chief risk factor for the intestinal type of gastric cancer [9]. It is initially acquired in childhood [10] and is believed to cause chronic active gastritis that progresses to CAG and IM [11]. The presence or absence of serum antibodies for *H. pylori* can also participate in the risk stratification of gastric adenocarcinoma [8,12].

Even though some efforts at developing screening or diagnostic methodologies to determine the presence and relevance of these conditions have been made, endoscopy alone is considered to be inaccurate to determine these changes and the 'gold standard' for the diagnosis of atrophic gastritis is histology obtained from biopsies during upper endoscopy [13,14]. Nonetheless, noninvasive strategies more attractive to asymptomatic individuals such as pepsinogen I and pepsinogen I/II ratio have also been described [15–19].

However, the cost-effectiveness of screening and follow-up of patients harbouring these conditions has been criticized and it is not well established, mostly requiring better estimates of the preferences and costs for patients, risk of progression and most importantly the prevalence of changes in gastric mucosa [20–22].

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To the best of our knowledge, only one review on the prevalence of CAG was published by Weck and Brenner [23], limited to only one database search and without any aggregated results. Therefore, the aim of this study was to systematically review the literature to assess the worldwide prevalence of gastric precancerous conditions in an aggregated manner by carrying out a meta-analysis of results and their relation with the gastric cancer incidence of the studied population; the secondary objectives were to study the differences in prevalence in terms of the methods of assessment, sex, age and *H. pylori* infection.

Methods

Selection of manuscripts

A sensitive search was performed to find out all relevant studies in terms of our research question using the PICO acronym (P-population, I-intervention, C-comparator, O-outcome) in different population settings (P) and subgroups (C), which is the prevalence of gastric precancerous conditions (atrophic gastritis and IM) (O) determined by either endoscopic or noninvasive methods (I) from the published literature. This systematic review follows the Preferred Reported Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [24].

Inclusion criteria were articles addressing gastric precancerous conditions (atrophic gastritis and IM), published in indexed journals up to March 2013, including primary cohort, retrospective or cross-sectional studies (review studies were used for cross-reference searching only). Searches were performed in PubMed, Scopus, Web of Knowledge and EBSCO Academic Search Complete using the following keywords: gastric cancer, atrophic gastritis, IM, gastric dysplasia, endoscopy, gastroscopy, biopsy and pepsinogen. These keywords were computed using Boolean operators in the following QUERY: '(gastric cancer OR atrophic gastritis OR intestinal metaplasia OR gastric dysplasia) AND (endoscopy OR gastroscopy OR biopsy OR pepsinogen)'. The only limit used was 'human only'.

After all references ($n = 6352$) were imported into a reference manager and duplicated records were discarded, the remaining records ($n = 4543$) were reviewed independently by title and abstract by two investigators against the inclusion criteria. The articles were then classified into six categories: (1) nonmedical, (2) non-gastroenterological, (3) nongastric, (4) gastric other than cancer, (5) gastric cancer and (6) gastric precancerous conditions.

Concordance between the two reviewers was measured by proportion of agreement and κ-statistics achieving a good agreement (68.7% proportion of agreement). Disagreements were resolved by joint discussion. Records classified as category (6) gastric precancerous conditions by both investigators ($n = 781$) were then considered eligible for full-text screening.

Cohort, case–control and cross-sectional studies were used for data extraction and all the studies, including the reviews ($n = 60$), were checked for cross-referencing not retrieved on databases search. Articles were then ruled out on the basis of exclusion criteria.

The reasons for exclusion were noncomprehensible language; case reports, opinion articles, experimental studies, population selected on the basis of previous conditions, relevant data missing, misclassification, same population of other studies, review articles after cross-referencing and full text not retrieved.

Data extraction

A data extraction sheet was produced. Information collected included domains such as study design, type of population (general or selected), demographics of the studied population, diagnostic methods and criteria used, *H. pylori* status and condition prevalence.

Analysis methodology

Some assumptions and simplifications had to be made for statistical and comparability purposes as the methods and definitions of the studies varied [25]. In studies where the two precancerous conditions were graded independently, results were assigned as either CAG or IM; extensive conditions were defined as the presence of CAG or IM not only in the antrum but also extending to the corpus; for cohort studies, only the baseline prevalence was used; when different prevalence scores were specified for antrum and corpus biopsies, with no global value presented, an overall prevalence was extracted as the one with the highest score; in studies comparing histological and endoscopic concordance, the prevalence used was the histological one; whenever possible, prevalence of conditions was dichotomized by age using the cut-off of 40 years old, which is the age below which the incidence of gastric cancers is negligible [1].

Studies were then divided into four groups: (a) biopsy-based studies in the general population, (b) biopsy-based studies in selected groups, (c) serology-based studies in the general population and (d) serology-based studies in selected groups. In samples categorized as 'selected groups', patients were mainly selected because of upper gastrointestinal symptoms (will also be called symptomatic or dyspeptic interchangeably), whereas those categorized as the general population were mostly based on mass screening studies and studies that used volunteers as controls (will also be called asymptomatic interchangeably).

Every country was also categorized on the basis of gastric cancer age-standardized rate incidence for both sexes retrieved from GLOBOCAN 2008. When subgroup analysis was carried out, populations were grouped on the basis of countries with a high incidence of gastric cancer (age-standardized rate $\geq 13.0/100\,000$) or countries with a low to moderate incidence of gastric cancer

(age-standardized rate < 13.0/100 000). We decided on this option instead of differentiating between Asian and White populations because even among these populations, the incidence rates are highly variable.

Statistical analysis

The worldwide prevalence of precancerous conditions was assessed in the different groups of incidence as a weighted proportion (extracted as randomized effect size) of the various values with its respective 95% confidence intervals. For this purpose, a preformatted datasheet developed by Neyeloff *et al.* [26] was used. Also, subgroup analyses were carried out addressing incidence of gastric cancer, sex, age, *H. pylori* infection and extension of conditions, although the majority of the records addressed only some of these issues. No statistical technique was used to deal with the missing values.

Results

Study demographic characteristics

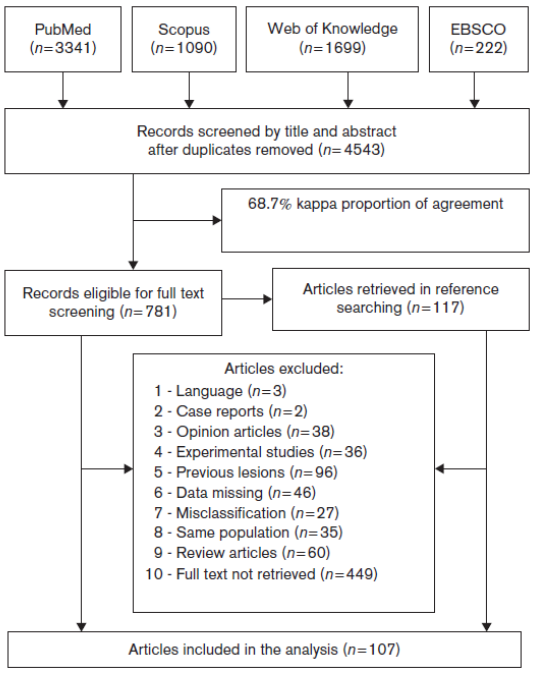
The literature sensitive search performed identified 783 records eligible for full-text screening (Fig. 1). After cross-referencing the retrieved records, 117 more articles were found. We had access only to 449 of the total 898 records (50%), with most unrecoverable records dating from before 1980. Of these 449 records, 343 were excluded on applying exclusion criteria and 107 articles [11,16,27–131] were finally included in the analysis. There were 99 endoscopy-based studies (23 in the general population and 76 in selected groups) and 35 serology-based studies (23 in the general population and 12 in selected groups).

In the endoscopy-based settings, 49 (49%) were dedicated to countries with a high incidence of gastric cancer (nine in the general population and 40 in selected groups), whereas 50 (51%) were respective to countries with a low to moderate incidence of gastric cancer (14 in the general population and 36 in selected groups). In this collection of studies, there is a good balance in the number of settings when comparing high-incidence with low-incidence areas.

In the serology-based settings, 25 (71%) addressed countries with a high incidence of gastric cancer (16 in the general population and nine in selected groups) and only 10 (29%) were respective to countries with a low to moderate incidence of gastric cancer (seven in the general population and three in selected groups), which could overestimate the worldwide prevalence of precancerous conditions.

There is a huge heterogeneity in the studies' designs, methods of selection and pathologic classifications. The majority of biopsy-based studies almost inevitably involved cross-sectional analysis of consecutive patients with upper gastrointestinal symptoms and upper endoscopy indication. However, serology-based settings studies mainly arise from health check-up surveys. Some endoscopic studies involved huge cohorts of over 1000 patients [30,48,68,85,88,130]. In serologic settings, these numbers were even larger, with some studies exceeding 5000 participants [122,123,127].

Fig. 1



Flowchart of articles' evaluation for inclusion in the study.

Only two settings [34,103] were aimed at paediatric populations. The overall mean age of all the studied groups could not be calculated because it was frequently missing, but if we consider it to be similar to the cases when it was available, the gross result was 50.6 years in endoscopic settings and 56.1 in serology-based studies.

The results of the total number of individuals studied are reported in Table 1. CAG and IM were assessed by endoscopy in a total of 20 912 and 30 960 individuals, respectively, whereas CAG was assessed by serology in 51 886 individuals. These numbers are considerably smaller in subgroup analysis as data were only available in some studies.

Global results on the prevalence of CAG and IM, plotted by incidence of gastric cancer, are presented as Forest plots in Figs 2 and 3. Some sort of linear relation between the prevalence of gastric precancerous conditions and incidence of gastric cancer by country is evident, but the huge heterogeneity of results is also noticeable.

Table 1 Prevalence rates for chronic atrophic gastritis and intestinal metaplasia according to the type of study and subgroup analysis

	Endoscopic studies								Serologic studies			
Subgroups	*n*	*s*	CAG (%)	95% CI	*n*	*s*	IM (%)	95% CI	*n*	*s*	CAG (%)	95% CI
Type of population												
General	13	4200	33.4	25.9–40.8	11	4736	25.0	19.5–30.5	23	47 294	23.9	18.6–29.2
Selected groups	40	16 712	31.6	25.9–37.3	43	26 224	25.4	21.4–29.3	12	4592	27.0	20.6–33.4
Gastric cancer incidence												
High incidence countries	26	12 870	41.7	35.4–48.1	31	21 707	28.1	23.8–32.4	23	34 122	29.1	25.9–32.2
Low to moderate incidence countries	27	8042	22.8	18.0–27.6	23	9253	21.7	16.1–27.4	8	17 764	9.8	7.3–12.3
Sex												
Men	11	3526	32.4	21.2–43.5	14	5879	22.7	17.4–28.0	17	27 190	24.9	18.4–31.5
Women	10	3528	28.1	19.0–37.2	12	6534	21.2	16.6–25.8	12	15 075	25.6	16.3–34.8
H. pylori infection												
Positive	33	9193	46.4	38.1–54.6	43	15 760	33.1	28.3–37.8	19	20 950	37.2	28.6–45.9
Negative	22	5260	17.1	11.9–22.3	29	8985	15.4	11.9–19.0	18	18 633	9.7	7.3–12.0
Age (years)												
≥ 40	14	8206	47.9	37.7–58.2	14	9436	32.5	25.6–39.5	8	24 445	25.5	17.6–33.4
<40	10	2959	21.6	11.5–31.6	11	4259	11.1	7.0–15.2	4	3342	13.5	1.4–25.6
Extensive precancerous conditions												
Global prevalence	27	8883	16.2	12.3–20.0	15	5866	13.2	8.9–17.4				
High incidence countries	13	3564	26.7	11.8–35.6	10	4275	16.2	9.7–22.8				
Low to moderate incidence countries	15	5319	7.3	5.6–9.0	5	1591	7.7	3.2–12.1				

The general population means asymptomatic patients; selected groups mean patients with upper gastrointestinal symptoms; high-incidence countries present an age-standardized rate of at least 13.0/100 000, whereas low to moderate incidence countries present an age-standardized rate less than 13.0/100 000 for both men and women.
CAG, chronic atrophic gastritis; CI, confidence interval; IM, intestinal metaplasia; *n*, number of studies; *s*, number of participants.

Prevalence of chronic atrophic gastritis and intestinal metaplasia

The results of prevalence rates are reported in Table 1. The prevalence of CAG was 33.4% in the general population and 31.6% in selected groups on the basis of biopsies. The rate was lower when serology was used: 23.9 and 27.0% in the general population and in selected groups, respectively. The prevalence of IM was 25.0 and 25.4% depending on the selection of participants (asymptomatic vs. dyspeptic).

Subgroup analysis

Gastric cancer incidence

When comparing the prevalence of precancerous conditions by incidence of gastric cancer, important differences are noticeable. In the general population, the prevalence of CAG is higher and statistically significant in high versus low-incidence to moderate-incidence countries when endoscopy is used (41.7 vs. 22.8%) or the estimation is by serology (39.1 vs. 9.8%). The difference in the prevalence of IM also retains a difference, but without statistical significance (28.1 vs. 21.7%).

Sex

The differences in the prevalence of CAG and IM between men and women are small and inconsistent. The prevalence of CAG was higher in men when endoscopy was used, but smaller in serologic studies.

Helicobacter pylori infection

An increase in the prevalence of CAG and IM was observed in *H. pylori*-infected individuals versus non-infected individuals. In *H. pylori*-positive individuals, the prevalence of CAG was 2.7 times higher (46.4 vs. 17.1%) in endoscopic estimation and 3.8 times higher in serologic diagnosis (37.2 vs. 9.7%). The prevalence of IM was also 2.1 times higher in infected individuals (33.1 vs. 15.4%).

Age

When comparing individuals of age below 40 and 40 years or older, estimates point to a two times higher prevalence in CAG (biopsy or serology based) and three times higher prevalence in IM for the older group. Statistically significant differences were found in endoscopic studies, but not serology-based estimates probably because of the small number of serologic studies.

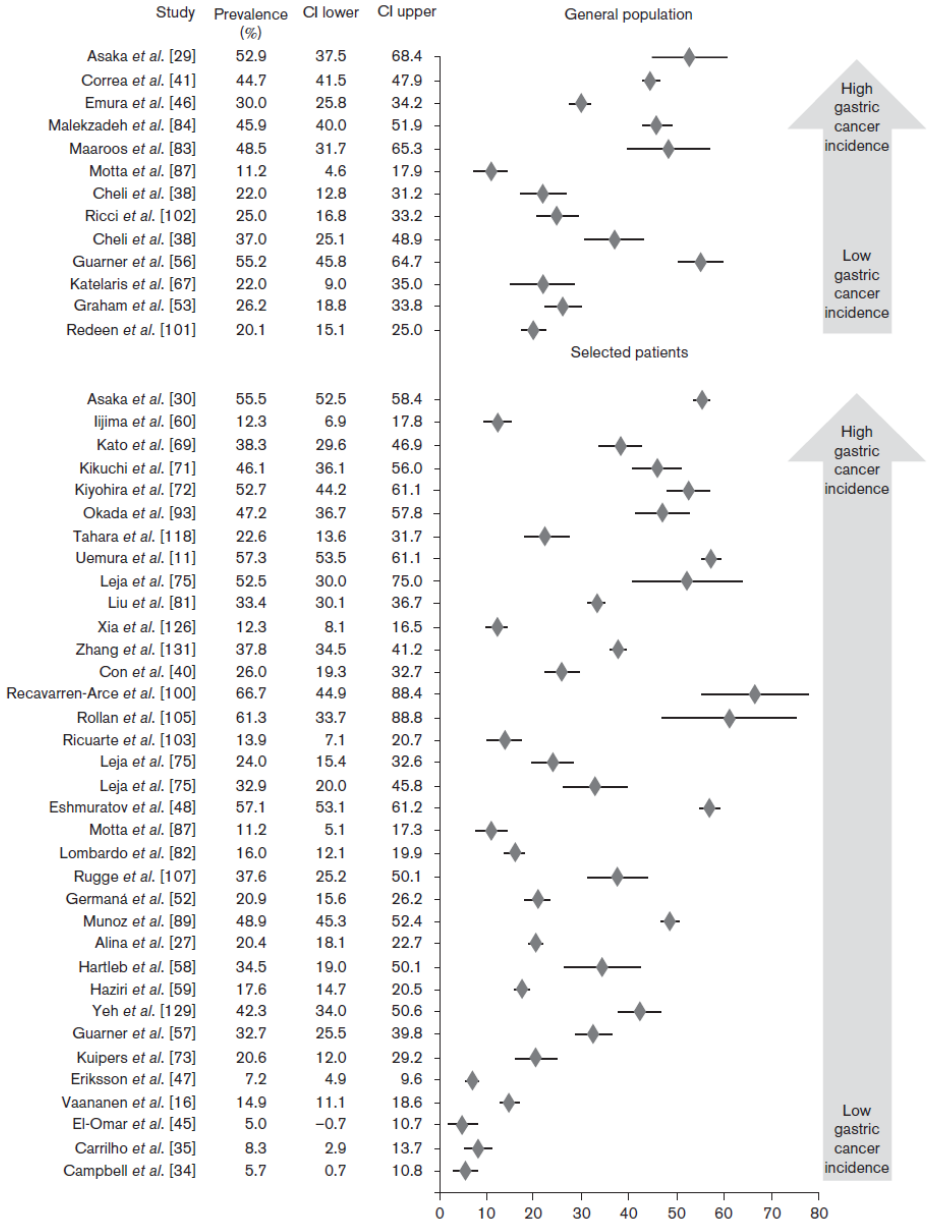
Extensive conditions

The estimated prevalence of extensive gastric precancerous conditions was 16.2% for CAG and 13.2% for IM in general. In countries with a low to moderate incidence of gastric cancer, 7.3% of individuals may harbour this high-risk phenotype, whereas in countries with a high incidence, it can reach up to 26.7% of the population (for CAG extensive conditions).

Discussion

Gastric precancerous conditions have a long-established significance in the development of gastric cancer and if detected and treated early, they could eventually alter its natural course [8,132]. Our results show that 32% of the general population may harbour CAG, whereas 25% may have IM when endoscopy with biopsies is performed. These values are not much different when comparing asymptomatic with dyspeptic individuals and these estimates are lower when using serology.

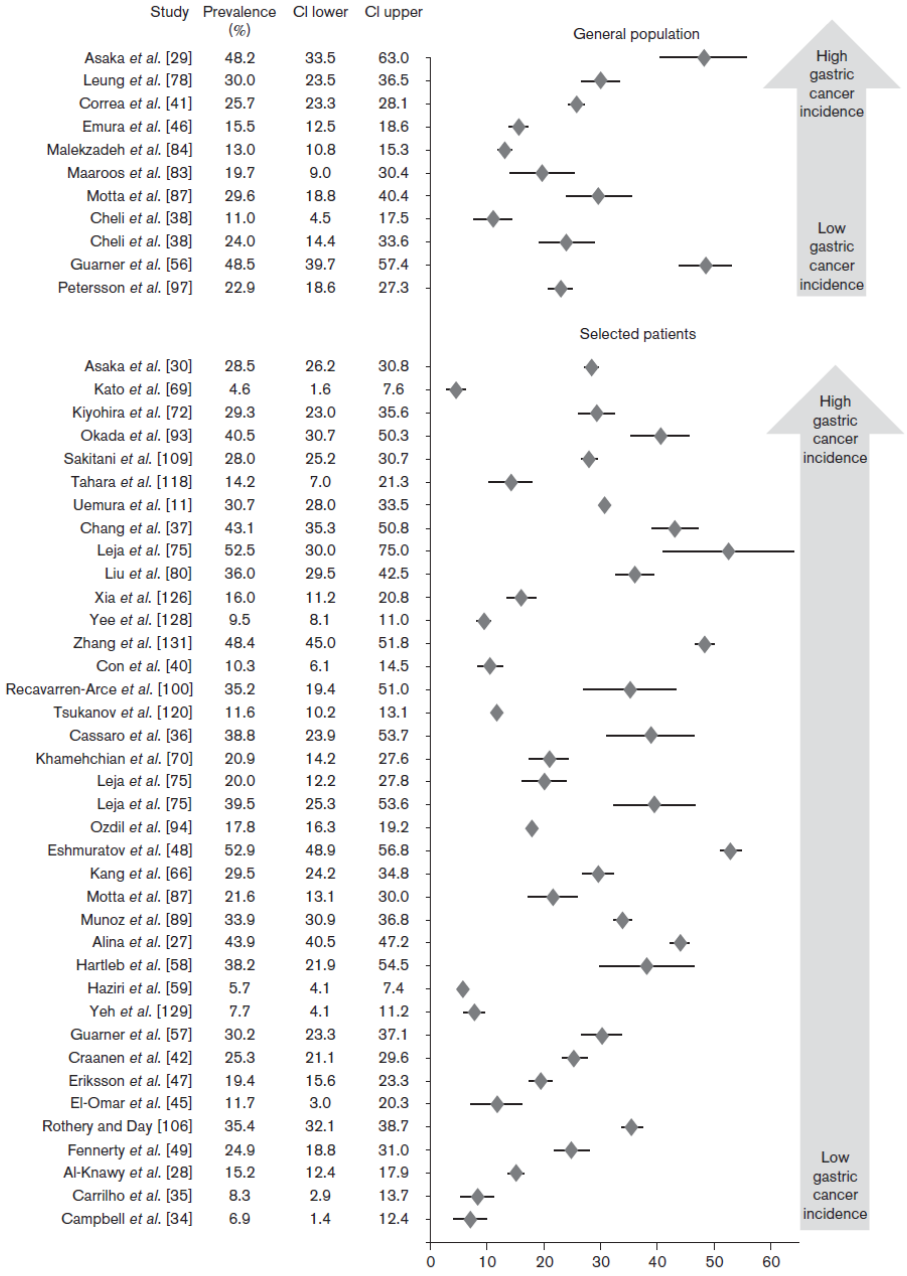
Fig. 2



Prevalence of chronic atrophic gastritis according to endoscopy-based studies. Upper cluster: studies in the general population (asymptomatic individuals); lower cluster: studies in selected groups (patients with upper gastrointestinal symptoms). Studies in each cluster are ordered by incidence of gastric cancer as retrieved from GLOBOCAN 2008. CI, confidence interval.

When the global results on the prevalence of CAG and IM were plotted by incidence of gastric cancer (Figs 2 and 3), some sort of linear relation between the prevalence of gastric precancerous conditions and incidence of gastric cancer can be seen, but the huge heterogeneity in results is even more noticeable. This can be because of various

Fig. 3



Prevalence of intestinal metaplasia according to endoscopy-based studies. Upper cluster: studies in the general population (asymptomatic individuals); lower cluster: studies in selected groups (patients with upper gastrointestinal symptoms). Studies in each cluster are ordered by incidence of gastric cancer as retrieved from GLOBOCAN 2008. CI, confidence interval.

factors, but the most significant are probably differences in the selection of patients or volunteers and the pathologic classifications criteria used as stated previously.

As predicted, when subgroup analysis was carried out, countries with a high incidence of gastric cancer, infection with *H. pylori* and age 40 years or older all had greater prevalence of precancerous conditions. The increase in the prevalence of CAG and IM in patients infected with *H. pylori* was expected and confirmed by our results. The prevalence of CAG was 2.7 times higher in endoscopic estimation and 3.8 times higher in serologic diagnosis in infected versus noninfected patients. These differences may be attributable to the sensitivity of serology to detect *H. pylori*.

When men and women were compared, the differences in the prevalence of CAG and IM were small and inconsistent and this lack of difference was not expected as men have almost two times higher incidence of gastric cancer than women [1]. Furthermore, when endoscopy was used, the prevalence of CAG was higher in men, but in serologic studies, it was slightly less than that in women. This could be just an artefact but could also suggest that cut-offs of pepsinogens might have to be optimized on the basis of sex, although differences in the production levels of men and women were not found in at least one validation study [15–19].

It is also noteworthy that when comparing countries with a high versus a low to moderate incidence of gastric cancer, the difference found in the prevalence was much greater for CAG (two to three times higher in endoscopy or serology studies) than for IM.

We also estimated the prevalence of extensive gastric precancerous conditions, which was only 7% in countries with a low to moderate incidence of gastric cancer, whereas in countries with a high incidence, it reached 16–27% for extensive IM and CAG, respectively. These estimates are important because, on the basis of recent guidelines, these patients harbour a high-risk phenotype and endoscopic surveillance should be offered [8].

Our study also exposes the huge heterogeneity in methods of assessment and classification criteria in the diagnosis of these conditions. The number of biopsies and their mapping are extremely diverse, ranging from only 1 to more than 10. Still, attending the multicentrality of the studies included and on examining the plots, we believe in a fine generalizability.

Some limitations cannot be excluded from this analysis. In terms of the design of this study, first, there is the issue of covering all the literatures. Even if our sensitive search and cross-referencing had gathered all the possible studies, we could not retrieve 50% of the total eligible records, most of them published more than 30 years ago. Second, we may have excluded important records. However, as this process was performed by two authors, this hypothesis is diminished. Third, as only one investigator extracted the data, it is prone to mistakes. The studies included ranged from 1980 to 2012 and, if the effect of these three decades spanning on the gastric conditions prevalence *per se* could be overlooked, the same could not be applied to either the evolution of diagnostic methods or the diagnostic classifications (e.g. Sydney System convention dates from 1992 to 1994, and the OLGA system was first evaluated in 2007). Finally, the fact that the great majority of the articles included covered only some of the topics necessary to the subgroup analysis (age, sex, etc) lessens the validity of the aggregation analysis carried out.

When comparing our study with a only similar one published by Weck and Brenner [23], we realize that they only addressed the prevalence of CAG (but not IM), only searched in one database (PubMed), limited the inclusion of English papers only, the review only included 41 studies and no aggregation of results was performed. However, the same problems on various definitions of CAG were found and also an increase in prevalence along with an increased age was detected.

In conclusion, there is a non-negligible large prevalence of gastric precancerous conditions in many countries. For individuals older than 40 years of age, the prevalence of IM is 32.5% and that of CAG is 47.9 or 25.5% when diagnosed by endoscopy or serology, respectively. In countries with a high incidence, it reached 16–27% for extensive IM and CAG, respectively, and on the basis of recent guidelines, this group of patients, who harbour a high-risk phenotype, should be diagnosed and further monitored endoscopically.

Nonetheless, our results need further validation by multicentre studies with standardized methodologies and, if confirmed, their use in economic studies may indicate an eventual cost-benefit of detection and surveillance of these conditions in asymptomatic individuals.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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Health-related Quality of Life and Utilities in Gastric Premalignant Conditions and Malignant Lesions: a Multicentre Study in a High Prevalence Country

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ABSTRACT

Background & Aims: A recent review of economic studies relating to gastric cancer revealed that authors use different tests to estimate utilities in patients with and without gastric cancer. Our aim was to determine the utilities of gastric premalignant conditions and adenocarcinoma with a single standardized health measure instrument.

Methods: Cross-sectional nationwide study of patients undergoing upper endoscopy (n=1,434) using the EQ-5D-5L quality of life (QoL) questionnaire.

Results: According to EQ-5D-5L, utilities in individuals without gastric lesions were 0.78 (95% confidence interval: 0.76-0.80), with gastric premalignant conditions 0.79 (0.77-0.81), previously treated for gastric cancer 0.77 (0.73-0.81) and with present cancer 0.68 (0.55-0.81). Self-reported QoL according to the visual analogue scale (VAS) for the same groups were 0.67 (0.66-0.69), 0.67 (0.66-0.69), 0.62 (0.59-0.65) and 0.62 (0.54-0.70) respectively. Utilities were consistently lower in women versus men (no lesions 0.71 vs. 0.78; premalignant conditions 0.70 vs. 0.82; treated for cancer 0.72 vs. 0.78 and present cancer 0.66 vs. 0.70).

Conclusion: The health-related QoL utilities of patients with premalignant conditions are similar to those without gastric diseases whereas patients with present cancer show decreased utilities. Moreover, women had consistently lower utilities than men. These results confirm that the use of a single standardized instrument such as the EQ-5D-5L for all stages of the gastric carcinogenesis cascade is feasible and that it captures differences between conditions and gender dissimilarities, being relevant information for authors pretending to conduct further cost-utility analysis.

Key words: gastrointestinal endoscopy – QoL – gastric cancer – intestinal metaplasia – atrophic gastritis.

Abbreviations: LYS: life-years saved, QALY: quality-adjusted life years, VAS: VAS, CI: confidence interval.

INTRODUCTION

Gastric adenocarcinoma is a health problem worldwide due to its high incidence and mortality rates, being the fourth most common malignancy and the second leading cause of cancer death [1]. Its prognosis is highly dependent on the stage at diagnosis but usually presents at an advanced stage requiring demanding treatments and costs and impairing quality of life (QoL), even for patients with a good prognosis [2].

In health economics studies, the clinical strategies adopted for a problem such as gastric cancer are compared by simultaneously addressing their differences in terms of both clinical benefits and the cost of achieving them [3]. Guidelines recommend conducting cost-utility analysis where the use of clinical benefits should be adjusted to patient preferences. Thus, life-years saved (LYS) may be adjusted to utilities in terms of QoL, quality adjusted life years (QALYs), meaning that 1 year of life is multiplied by a utility factor between 1 and 0, providing different values for each single year of life, resulting in an utility value that will vary between 1 QALY (one year with perfect

QoL) and 0 (death, by definition). These guidelines also suggest that community preferences should be used instead of patient preferences [4-6].

In a recent systematic review of the literature on economic studies relating to gastric cancer our group found that authors mostly used patient preferences instead of the recommended community preferences and that utilities were obtained by using several measurement instruments, including questionnaires that were specifically created for comparing gastric cancer treatments that should not be compared to utilities in the general population. Also, models tend to use utilities reported in other studies, usually conducted in countries different from the population in the model, where health valuations might have given different results [7]. Utilities obtained in a population with a single questionnaire could be very suitable for conducting cost-utility analysis on the gastric cancer problem since they would provide comparative utilities for all stages of the gastric cancer cascade from an asymptomatic population to gastric cancer patients [8].

Thus, the aim of our study was to perform a cross-sectional study to obtain utilities from a population that would include patients without gastric lesions and also with all kinds of upper gastrointestinal diseases, including patients with all ranges of gastric premalignant conditions, patients submitted to endoscopic treatments and patients with gastric cancer submitted to all available treatments [9-11].

METHODS

This cross-sectional study was performed in 8 Portuguese hospitals over 6 months, between 2012 and 2013, by delivering a QoL related questionnaire to patients already scheduled for routine upper gastrointestinal endoscopic examinations. The questionnaire was the Portuguese version of the EQ-5D-5L and the reference test for the diagnosis was the gastroenterology diagnosis, including the histopathology result when applicable. The planning, development and report of the study are in accordance with the STROBE statement for reports on observational studies [12, 13].

Portugal is considered to have a high-incidence of gastric cancer according to the GLOBOCAN definition by presenting an age-standardized incidence rate of 13.7 per 100,000 [14]. From all over the country, including north, centre, south of Portugal and the two major cities of Lisbon and Porto, 8 gastroenterology departments in 8 different hospitals comprising 2 academic hospitals, 3 oncology centers and 3 regional hospitals, were invited and agreed to participate. Consecutive patients were included in each hospital for 3 months and each patient scheduled for an upper endoscopy procedure was invited to complete a questionnaire before the examination to self-report their QoL on the day of the examination.

The outcomes obtained were the self-reported answers to the questionnaire, providing a measure of QoL on the day of the upper endoscopy procedure, plus the diagnosis provided by the attending gastroenterologist, which can be based on the endoscopic diagnosis, pathology result or known medical history, as applicable. To allow for generalization of results, a selection of hospitals was made in order to obtain a heterogeneous population in terms of both geographic location and hospital setting.

The only inclusion criteria were the completion of an already scheduled upper endoscopy along with a voluntary signed informed consent specific to the study. Exclusion criteria were emergency examinations, failure to provide informed consent or any contraindication for upper endoscopy.

The study was approved by the Portuguese Data Protection Authority (Authorization 4982/2012) after granting permission for the compilation of multicenter national data, and also by each hospital Ethics Committee. Confidentiality of all records was ensured by removing the names of patients, doctors and nurses from the reports before they were sent to the main investigator.

Selection bias was minimized by asking all institutions for a consecutive sample, having a very broad inclusion criteria setting and carrying out the study in the whole country in hospitals with very different population characteristics, for at least 3 months in order to allow the inclusion of most types of upper gastrointestinal diseases.

QoL questionnaire

The questionnaire used was the EQ-5D-5L developed by the EuroQol Group which is a standardized measure to provide utilities for clinical and economic appraisal [15]. This questionnaire was chosen because it can be applied to a wide range of health conditions and treatments, provides a simple descriptive profile and a single index value for each health status, has been validated over many years in a number of populations and settings, is the most recent version of the EuroQol EQ-5D questionnaire and is available in several translations, including an already validated and reliable Portuguese version [16].

The EQ-5D-5L questionnaire comprises a descriptive system and a visual analogue scale (VAS). The descriptive system has 5 dimensions: mobility, self care, usual activities, pain/discomfort and anxiety/depression, and each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems (the former EQ-5D had only 3 choices per question, being called EQ-5D-3L). Respondents are asked to indicate their health state by marking the box against the most appropriate statement in each of the 5 dimensions. The digits for the 5 dimensions can be combined in a 5-digit number describing the respondent's health state. Health states defined by the EQ-5D-5L descriptive system were converted into a single index value to calculate utilities, according to the recommendations of the EuroQol Group [17].

The similar EQ-5D-3L system was only recently validated in the Portuguese population, by setting preferences for the general population using the time trade-off technique and also developing population norms [18, 19]. Because currently there is no validated method to transform utilities from the EQ-5D-3L to the EQ-5D-5L systems, we used the Spanish EQ-5D-5L utilities. From the available options, the Spanish utilities are the most similar, providing a Pearson's correlation coefficient of r=0.946 for both EQ-5D-3L population norms [18].

The VAS records the respondent's self-rated health on a 20 cm vertical VAS, with endpoints labeled "the best health you can imagine" and "the worst health you can imagine".

A correctly completed questionnaire was defined as a questionnaire with each of the 5 multiple choice questions for the descriptive system completed with a single cross and a clear and readable number in the VAS.

Endoscopic procedure

For each questionnaire the corresponding diagnosis was obtained from the upper endoscopy result. Upper endoscopy is considered the ideal procedure for the diagnosis of upper gastrointestinal diseases due to its widespread availability, improved accuracy for most diseases, relatively minor invasiveness and possibility of performing diagnostic and/or therapeutic procedures [20-24]. There were no specific inclusion or exclusion criteria based on patient diagnosis, endoscopists' experience, type of endoscopic facility or scope. Biopsies were done as deemed necessary, but not specifically for participation in the study.

Sample size and statistical analysis

For the sample size calculation, an estimate of at least 44 patients per group would be needed for a level of significance of 0.05 and a power of 0.80, based on previous reports that for normal patients the utility score was 0.90, for patients with premalignant conditions 0.70 and for patients with gastric cancer 0.50. We aimed at obtaining 100 patients for each of these groups, to ensure that confidence intervals would not be wider than ±0.10, in order to achieve statistically significant differences between utilities [25].

Results are reported as means and 95% confidence interval (CI) for continuous variables and percentages for proportions. For comparative analysis the Student's *t*-test was used for continuous variables according to their normal distribution and the Pearson chi-square test for dichotomous variables. A two-sided p value <0.05 was considered to be statistically significant. Results were analyzed in subgroups for confounding factors such as age or gender but not for co-morbidities. No data was missing from the retrieved questionnaires.

RESULTS

All subjects scheduled for an upper endoscopy were invited and after exclusions for several factors such as refusing to

Table I. Main patient characteristics and utilities according to stages of the gastric carcinogenesis cascade and most relevant upper gastrointestinal diseases

	n (%)	EQ-5D-5L mean (95% CI)	VAS mean (95% CI)
Patients	1,434		
Male gender	755 (52.6)		
Age ≥ 50 years	1,063 (74.1)		
Participating hospital: n (% global), (% gastric cancer)			
Portuguese Oncology Institute of Coimbra	353 (24.6), (20.7)		
Portuguese Oncology Institute of Lisbon	294 (20.5), (9.5)		
Santa Luzia Hospital, Viana do Castelo	205 (14.3), (4.4)		
Santo António General Hospital, Porto	168 (11.7), (1.8)		
Hospital Unit of Portimão	142 (9.9), (4.9)		
Coimbra's University and Hospital Center	134 (9.3), (8.9)		
Portuguese Oncology Institute of Porto	69 (4.8), (20.3)		
West Lisbon Hospital Centre	69 (4.8), (2.9)		
No gastric lesions	678 (47.3)	0.78 (0.76-0.80)	0.67 (0.66-0.69)
Gastric premalignant conditions (gastritis, atrophy, intestinal metaplasia)	391 (27.3)	0.79 (0.77-0.81)	0.67(0.66-0.69)
Gastric adenocarcinoma	148 (10.3)	0.77 (0.73-0.81)	0.62 (0.59-0.65)
Treated by:			
- Mucosectomy	17 (1.2)	0.78 (0.63-0.92)	0.62 (0.54-0.70)
- Surgery	69 (4.8)	0.77 (0.71-0.82)	0.62 (0.57-0.67)
- Chemo/Radiotherapy	38 (2.6)	0.83 (0.77-0.89)	0.63 (0.57-0.70)
Present carcinoma	24 (1.7)	0.68 (0.55-0.81)	0.62 (0.54-0.70)
Other lesions*	731		
Hiatal hernia	155 (10.8)	0.77 (0.73-0.80)	0.66 (0.63-0.69)
Esophagitis	83 (5.8)	0.79 (0.74-0.74)	0.69 (0.65-0.73)
Peptic ulcer	36 (2.5)	0.78 (0.72-0.84)	0.62 (0.56-0.69)
Barrett's esophagus	28 (1.9)	0.79 (0.67-0.90)	0.74 (0.66-0.80)

*Other lesions stand for all lesions in the esophagus, stomach or duodenum except for gastric premalignant conditions or gastric adenocarcinoma. Only the most frequent reported are presented.
Legend: EQ-5D-5L: EuroQol EQ-5D-5L questionnaire; VAS scale: visual analogue scale of the EQ-5D-5L questionnaire; CI: confidence interval.

Table II. Utilities according to stages of the gastric carcinogenesis cascade in patients aged 50 or over, by gender

	Age ≥ 50 years		p	Age ≥ 50 years		p
Scale	EQ-5D-5L mean (95% CI)			VAS mean (95% CI)		
Gender	Male	Female		Male	Female	
No gastric lesions	0.78 (0.76-0.81)	0.71 (0.67-0.75)	0.01	0.65 (0.63-0.68)	0.63 (0.60-0.66)	0.19
Gastric premalignant conditions	0.82 (0.79-0.85)	0.70 (0.66-0.74)	0.01	0.69 (0.66-0.73)	0.60 (0.57-0.63)	0.01
Gastric adenocarcinoma	0.78 (0.73-0.83)	0.72 (0.65-0.79)	0.15	0.62 (0.58-0.67)	0.59 (0.54-0.64)	0.33
Treated by:						
Mucosectomy	0.77 (0.50-1.00)	0.70 (0.33-1.00)	0.69	0.61 (0.48-0.73)	0.52 (0.42-0.62)	0.25
Surgery	0.79 (0.72-0.87)	0.71 (0.62-0.80)	0.18	0.63 (0.55-0.70)	0.58 (0.51-0.66)	0.42
Chemo/Radiotherapy	0.85 (0.79-0.91)	0.76 (0.60-0.92)	0.19	0.64 (0.55-0.72)	0.60 (0.50-0.70)	0.59
Present carcinoma	0.70 (0.42-0.97)	0.66 (0.49-0.83)	0.79	0.66 (0.48-0.84)	0.60 (0.50-0.71)	0.52

Legend: EQ-5D-5L: EuroQol EQ-5D-5L questionnaire; VAS: visual analogue scale of the EQ-5D-5L questionnaire; CI: confidence interval; *: Student's *t*-test.

participate, endoscopy not performed, declined to complete questionnaire or incomplete data, 1,434 questionnaires out of 1,886 were completed correctly achieving a participation rate of 76%. The characteristics of patients with incomplete questionnaires were not possible to access because in most cases the main data missing were the clinical issues such as age, gender or diagnosis and not the fulfilling of the EQ-5D-5L questionnaire.

The main patient characteristics and results for the most relevant upper gastrointestinal diseases, including all stages of the gastric carcinogenesis cascade, are reported in Table I. Participants were 53% male with a mean age of 59 years. The examination was considered normal in only 24% of cases, and most relevant abnormalities detected were gastric premalignant conditions such as gastritis, atrophy or intestinal metaplasia and esophageal conditions such as hiatal hernia or esophagitis. There were no relevant differences between participating institutions in terms of patients' diseases, except for there being more cancer patients in the Oncology Centers, as expected (13.7% vs. 4.7%, p=0.01).

In terms of the 5 dimensions of the EQ-5D-5L questionnaire, 75% to 93% of participants said they had no or only slight problems in all five dimensions with better score for self-care such as washing or dressing themselves and only 2.2% to 6.1% reported severe to extreme problems with worst score for usual activities such as work, study, housework, family or leisure. Anxiety was moderate to extreme in 21% of patients without relevant differences among groups (no lesions 21%, premalignant conditions 23%, gastric cancer 18%).

Although the numbers of included questionnaires vary and are related to a diverse prevalence of these diseases in the general population, VAS scores were consistently lower than the EQ-5D-5L utilities, regardless of organ or severity of disease, in all conditions analyzed.

Utilities for all stages of the gastric cancer cascade of carcinogenesis, with subgroup analysis by gender and including only patients aged 50 or over are summarized in Table II. This subgroup analysis is justified by the fact that this is the population (≥50 years) which is usually considered to be cost-effective to offer endoscopic screening or surveillance strategies [26]. No comparison between <50 and ≥50 years was made due to the huge differences between groups in terms of available questionnaires 371 vs. 1063 and gastric cancer cases 11 vs. 137.

Overall scores demonstrated that the two scales provided similar results for patients without gastric lesions or with gastric premalignant conditions with utilities lower for patients who had present gastric cancer than for patients without gastric lesions or those with premalignant conditions (0.68 versus ≥0.77, p=0.09).

When adjusting for gender and including only patients aged 50 or above, the results consistently show that utilities were lower for women than for men. This dissimilar scoring for males and females achieves a statistically significant difference in some normal or premalignant conditions in both scales.

DISCUSSION

This cross-sectional study of patients scheduled for an upper endoscopy procedure provided utilities and self-reported QoL data for a nationwide population with a validated questionnaire in a sample of patients embracing all stages of the carcinogenic cascade for gastric adenocarcinoma. These results, although specific to the studied population, might be relevant to further cost-utility studies in gastric cancer as a recent systematic review showed that utilities were relevant in several studies for the final results of the economic analysis, namely QoL in diseased patients and also after treatments for cancer [7, 8].

Utilities measured by the EQ-5D-5L questionnaire showed similar scores for patients without gastric lesions (0.78), patients with premalignant conditions (0.82) and patients with previously treated gastric cancer (0.77-0.79) but lower values

Table III. Comparison of the current study with published cost-utility studies on gastric cancer and respective references used for utilities valuation

Present study	1. Values for the asymptomatic population 2. Normal is different from 1 3. Values for all gastric premalignant conditions (gastritis, atrophy, intestinal metaplasia and dysplasia) 4. Values for endoscopic treatment (mucosectomy) 5. Values for gastric cancer patients in 3 different stages of treatment (surgery, chemotherapy and/or radiotherapy and best supportive care) 6. Different evaluations for men and women

Other studies (1st author, year, country)	Intervention	Utilities references	Utility values from references	Comment on references used
Xie, 2008 [31] Xie, 2008 [32] Singapore	Screening (serology) and treat *H. pylori* or Screening (UBT) and treat *H. pylori*	Wang Q, et al. 2003 [38]	*H. pylori* non-infected 1.00 (0.95-1.00) *H. pylori* infected 0.90 (0.80-1.00) Gastric cancer 0.38 (0.13-0.65)	Normal is 1 No values for population No values for premalignant gastric conditions Just one value for gastric cancer
Xie, 2009 [33] Canada	Screening (Stool Ag) or Screening (serology) or Screening (UBT†)	Delaney BC, et al. 2008 [39] Ajani JA, et al. 2007 [40]	*H. pylori* uninfected 0.83 (0.80-0.86) *H. pylor*i infected 0.83 (0.80-0.86) Gastric cancer 0.55 (0.47-0.63)	No values for population No values for premalignant gastric conditions Same value for uninfected and infected patients Just one value for gastric cancer
Yeh, 2009 [37] China	Screening (serology) and treat *H. pylori* or Universal treatment	Mathers CD, et al. 2000 [41] Gold MR, et al. 1998 [25]	Normal gastric mucosa 0.56–0.94 Gastritis 0.56–0.94 Atrophy 0.56–0.94 Intestinal metaplasia 0.56–0.94 Dysplasia 0.56–0.94 Symptomatic gastric cancer 0.49 (0.17–0.79)	No values for population Same value for all premalignant lesions Just one value for gastric cancer
Dan, 2006 [35] Singapore	Endoscopy every 2 years	Glimelius B, et al. 1995 [42] Blazeby JM, et al. 2004 [43]	Stages I and II (surgery) 0.65 Stage III (chemo radiotherapy) 0.4 Stage IV (palliative care) 0.5	No values for population No values for premalignant gastric conditions
Gupta, 2011 [30] USA	Endoscopy + Barrett's surveillance or Endoscopy	Inadomi JM, et al. 2003 [44] Rubenstein JH, et al. 2007 [45] Inadomi JM, et al. 2009 [46]	Cancer 0.5-0.75 Post-gastrectomy state 0.97 (0.8-1)	No values for population No values for premalignant gastric conditions Value for cancer as a whole
Zhou, 2011 [34] China	Serum pepsinogens + Endoscopy	World Health Organization QoL (WHOQOL)- BREF questionnaire [47]	Healthy residents 1.00 Gastric cancer patients 0.68-0.66	Normal is 1 No values for premalignant gastric conditions Just one value for gastric cancer
Dinis-Ribeiro, 2007 [29] Portugal	Yearly magnification chromoendoscopy + Serum Pepsinogens	Kaptein AA, et al. 2005 [48]	Death 0 Chemotherapy 0.1–0.3 Surgery 0.4–0.8 Mucosectomy 0.8–0.95	No values for population No values for premalignant gastric conditions
Yeh, 2010 [36] USA	Endoscopic surveillance every 1, 5 or 10 years	Hanmer J, et al. 2006 [49] Gold MR, et al. 1998 [25]	Age-related quality weight 0.78-0.93 Gastric cancer 0.49 (0.17-0.79)	No values for population No values for premalignant gastric conditions Just one value for gastric cancer

Legend: UBT: Urea Breath Test; Ag: Antigen.

for patients with present carcinoma (0.66) and for the same clinical situations the EQ-5D-5L scores were always lower for female than for male.

To the best of our knowledge this study is the first providing utilities for all stages of the gastric cancer cascade using a single health utilities measurement instrument. The study provides very useful information for authors conducting cost-utility analysis by incorporating utilities in their Markov models [8].

Our main conclusion and contribution to the actual medical practice is that the use of a single standardized instrument like EQ-5D-5L for all stages of disease is feasible, that it captures differences among stages (no lesions vs. premalignant conditions vs. present cancer) and adjustments by gender are relevant when incorporating utilities in economic models.

A second relevant conclusion is that the utilities varied between different stages of disease in a much narrower set of values (around 0.6 for cancer vs. 0.8 for no cancer) than previously reported in other models (around 0.3 vs. 0.9 for the same groups), raising the concern that utilities valuation by using different questionnaires for different stages of disease, as has been done in other models, might overvalue real differences and overestimate the final economic conclusions among strategies.

Advantages of this study is that it includes patients on a nationwide basis, from general and teaching hospitals, and oncology centers, it covers more than 1400 reports, providing more than 100 patients in each subgroup (no lesions vs. premalignant lesions vs. gastric cancer) and utilities are linked to a medical diagnosis confirmed by a doctor after performing an endoscopy with biopsies when needed. In addition, by including a range of upper gastrointestinal diseases it means that utilities of the general population with the same background are comparable.

To prevent selection bias as possible, a variety of hospitals from all over the country were selected, participants were consecutive and unselected, no change in routine practice was necessary and the analysis of the results was blinded. Also, anxiety caused by endoscopy that could influence the results in terms of utilities was consistently similar among groups.

When comparing our study results to the study by Gold et al used for the sample size calculation, utilities values in other diseases returned similar results to ours: for esophageal problems 0.70 vs. 0.69 and for peptic ulcer 0.66 vs. 0.62. Also, in a study performed in our country using the same EQ-5D questionnaire in gastrointestinal patients (n=125), utilities for gastric cancer (n=5) ranged between 50 and 70, including our result of 0.62 [27].

The finding of different utilities between male and female is in accordance with a similar study in Portugal and also in other countries, confirming that this consistent result should be incorporated in cost-utility models [19, 28].

The relevance of the present study to the already available literature comes from the existence of several problems within the methodology of cost-utility studies published. We think these problems might have been overcome with the present study (see Table III) [25, 29-49]. Xie et al, Dan et al, Gupta et al, Zhou et al, Dinis-Ribeiro et al did not use values for the asymptomatic population; Xie et al and Zhou et al used 1 as the value for the normal population; only Yeh et al had values for premalignant gastric conditions; only Dinis-Ribeiro et al had values for the post mucosectomy stage; only Dan et al and Dinis-Ribeiro et al presented more than a single value for all gastric cancer patients, irrespective of the type of treatment performed and only two authors used a single reference to obtain the utilities for their models: the study by Wang Q et al that is in Chinese and not available to most clinicians, and the study by Dinis-Ribeiro et al that used a systematic review of studies embracing several different questionnaires on patients with diagnosed or treated gastric cancer. Finally, not a single model evaluated differently the male and female utilities.

We think that it is very important to use a single validated instrument for all stages of disease so that utilities among different stages are not overestimated by the use of different and not comparable questionnaires. Also, as suggested by the guidelines, utilities valuation should come from community preferences as ours did and not only from diseased patients [4].

The results of our study have implications on the interpretation of previous models on endoscopic surveillance of gastric premalignant conditions because the wider utilities' values used by others could result from using different questionnaires for different clinical situations, thereby overestimating differences in utilities and the final model outcome between strategies.

This study has some limitations that need to be addressed: in one hospital the questionnaires were completed after performing upper endoscopy while in all the others this was done before the examination and, although it is expected that answers to items such as mobility, self-care, usual activities and pain or discomfort are not influenced by the examination, the item on anxiety might be influenced by whether the questionnaire was completed before or after the endoscopy. Also, in the absence of standard health values for the Portuguese population for the validated questionnaire used (EQ-5D-5L) we used values for the Spanish population. Although the populations are different and their valuation of QoL will be dissimilar, the closest possible proximity and geographic location should provide some degree of similarity.

CONCLUSIONS

Our results confirm the applicability of using a single standardized instrument such as EQ-5D-5L for all stages of disease as it captures differences in utilities among stages and gender and wider differences among stages reported in previous models might result from the use of different instruments and overestimate real dissimilarities. These conclusions may be relevant to further cost-utility analysis in gastric cancer and should be incorporated by authors in their models.

Conflicts of interest: No conflicts to declare for all authors.

Authors' contribution: M.A., F. R.G. and M.D-R. planned and conducted the study, interpreted data and drafted the manuscript. All the authors included patients, provided a critical revision of the manuscript and approved the final manuscript version.

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Cost-Utility Analysis of Endoscopic Surveillance of Patients with Gastric Premalignant Conditions

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Keywords
Atrophic gastritis, cost-benefit analysis, cost-effectiveness, gastric neoplasm, gastrointestinal endoscopy.

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Background: Progression of extensive gastric premalignant conditions to cancer might warrant surveillance programms. Recent guidelines suggest a 3-yearly endoscopic follow-up for these patients. Our aim was to determine the cost utility of endoscopic surveillance of patients with extensive gastric premalignant conditions such as extensive atrophy or intestinal metaplasia.
Materials and Methods: A cost-utility economic analysis was performed from a societal perspective in Portugal using a Markov model to compare two strategies: surveillance versus no surveillance. Clinical data were collected from a systematic review of the literature, costs from published national data, and community utilities derived from a population study by the EuroQol questionnaire in terms of quality-adjusted life years (QALY). Population started at age 50, for a time horizon of 25 years and an annual discount rate of 3% was used for cost and effectiveness. Primary outcome was the incremental cost-effectiveness ratio (ICER) of a 3-yearly endoscopic surveillance versus no surveillance for a base case scenario and in deterministic and probabilistic sensitivity analysis. Secondary outcomes were ICER of 5- and 10-yearly endoscopic surveillance versus no surveillance.
Results: Endoscopic surveillance every 3 years provided an ICER of € 18,336, below the adopted threshold of € 36,575 which corresponds to the proposed guideline limit of USD 50,000 and this strategy dominated surveillance every 5 or 10 years. Utilities for endoscopic treatment were relevant in deterministic analysis, while probabilistic analysis showed that in 78% of cases the model was cost-effective.
Conclusions: Endoscopic surveillance every 3 years of patients with premalignant conditions is cost-effective.

Gastric cancer is a worldwide problem due to its high incidence and mortality because, unfortunately, in most countries, patients still present in advanced stages of the disease. When cancer is diagnosed so late, patients are offered treatments such as surgery, chemotherapy or radiotherapy that are expensive, impair their quality of life and still offer a poor prognosis, with an overall 5-year survival rate below 25% [1–3].

To prevent late detection of the disease, health authorities should choose between primary prevention programs such as *Helicobacter pylori* screening and eradication or secondary prevention programs like population screening or surveillance of patients at high risk for development of the disease, preferably supported by economic analysis for the strategy adopted [4–7].

Secondary prevention is usually based on endoscopy because it is widely available, accurate, involves relatively minor invasiveness and offers the chance of simultaneously performing diagnostic biopsies and/or therapeutic procedures as there is no valid widely available alternative [8,9]. The choice of a screening or a surveillance strategy depends on the incidence of the disease and, while in Japan endoscopic screening is considered cost-effective, in most countries, the balance between endoscopic and gastric cancer treatment costs makes screening not cost-effective [5,6,10,11].

For the intestinal type of gastric adenocarcinoma, a well-defined cascade of lesions ranging from atrophy to intestinal metaplasia and dysplasia might progress to the development of invasive cancer. The surveillance of

patients with these conditions might allow the endoscopic treatment of dysplastic lesions or the detection of early invasive cancers that are treatable with less demanding and cheaper treatments with better prognosis [7,12–14].

Recently published European guidelines suggest a 3-yearly endoscopic surveillance for the follow-up of patients with high-risk conditions of progression, such as the presence of extensive atrophy or intestinal metaplasia, [5,6] but only three studies have been published so far on the surveillance of patients with extensive atrophy or intestinal metaplasia. They report conflicting results on the cost-effectiveness of this strategy, with one concluding for the cost-effectiveness of annual surveillance of these patients, whereas the other two find incremental cost-effectiveness ratios above the accepted threshold, probably related to different assumptions on the progression rates of these conditions [15–17].

In light of this, our study aim was to perform an economic analysis on the secondary prevention of gastric adenocarcinoma by endoscopic surveillance of patients at high-risk of progressing because of extensive atrophy lesions or intestinal metaplasia detected after an opportunistic endoscopy with biopsies. The study was designed for the Portuguese population because Portugal has the highest incidence of the disease in Western Europe [18].

Methods

Study Population

Portuguese adults at high risk of developing gastric cancer because of extensive atrophy or intestinal metaplasia conditions were studied by a cost-utility analysis that incorporates utilities obtained for the Portuguese population in a preference-based community questionnaire, along with benefits in terms of survival. This high-risk population at start of the model is assumed to be detected by a first endoscopy as the result of opportunistic screening with biopsies. Screening methods such as pepsinogens were out of the aim of the present model that deals only with surveillance strategies [9,19,20]. A societal perspective was adopted by including the costs to the health system, patients, families and employers, thereby representing the public interest rather than that of any specific group, in accordance with the recommendations for reporting cost-effectiveness analyses [21–23].

The alternative option after an endoscopy with biopsies diagnosing extensive conditions was the no surveillance strategy, which is adopted in those countries where low incidence precludes any screening or surveillance strategies and where studies such as ours are awaited to define the economic rationale for surveillance of these high-risk patients, as suggested by recent guidelines [5,6].

Model Structure

A Markov model was chosen to incorporate several states of disease and all available treatment effects possible, plus their transition probabilities, as shown in Fig. 1. The alternatives being compared come before each Markov tree that was conceived with a 1-year cycle length. Health states presented in the model are the premalignant state, cancer state, postcancer state, and death. Every branch corresponds to an option for every state (circle), and Markov cycles start at the beginning of each starting branch from the premalignant state (circle with an M). On the far right are the terminal states (triangles) for the Markov cycles and patients at these stages return to the beginning of the next cycle after a 1-year cycle, except for the death stage (the only absorbing health state). The major difference between both arms (surveillance vs no surveillance), after a first opportunistic endoscopy, results from the fact that with endoscopic surveillance almost all progression cases will be detected as dysplasia amenable to endoscopic submucosal dissection, while invasive cancers detected after 3 years and missed by the previous endoscopy should will be in earlier stages than progression without surveillance.

To report this economic evaluation, we adopted the suggestions of four guidelines, two for authors and peer reviewers of economic submissions, and two for good practice in decision-analytic modeling in health technology assessment [24–31]. The software used was TreeAge Pro 2009 (TreeAge Software, Williamstown, MA, USA).

The starting age for surveillance after a first endoscopy was set at 50 and the surveillance span was 25 years, until the age of 75, similar to the suggested lifespan of the European colorectal cancer screening programe [32].

The currency used is the Euro (€) and costs are given in 2013 prices. Prices from previous years, that is daily costs for in-patients with data from 2009, were adjusted for inflation with a conversion tool from Pordata [33]. A discount rate of 3% was incorporated in all cost and effectiveness data, ranging in the sensitivity analysis between 0 and 5% in accordance with published guidelines [21–23,34].

Clinical Data

Data on effectiveness were obtained from a recent systematic review of all the economic studies published so

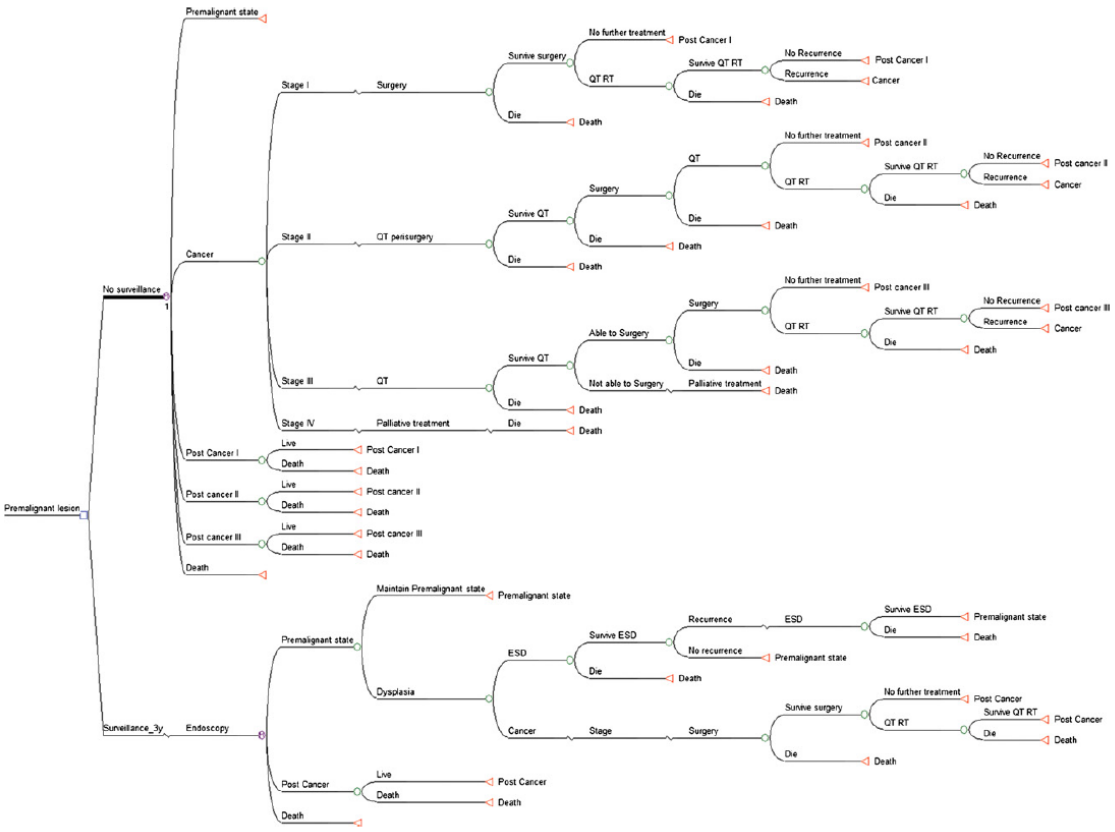

Figure 1 Markov model for comparison of endoscopic surveillance every 3 years versus no surveillance. Tree diagram representing all possible options for patients with premalignant gastric lesions, if submitted to a 3-yearly endoscopic surveillance protocol or without surveillance. Every branch corresponds to an option for every state (circle) and Markov cycles start at the beginning of each starting branch from the premalignant state (circle with an M). On the far right are the terminal states (triangles) for the Markov cycles and patients at these stages, except for the Death stage, return to the beginning of the next cycle after a 1-year cycle. ESD – endoscopic submucosal dissection; QT – chemotherapy; RT – radiotherapy.

far on the subject of gastric cancer screening or surveillance. At the same time, we carried out an extensive review of the available literature for systematic reviews or meta-analyses for the best available estimates for each transition probability (and not single studies) in terms of progression of conditions, distribution by cancer stage, efficacy of treatments, adverse events, and disease-specific survival [7].

An example of a full electronic search strategy for the PubMed search would be: "(cost benefit [Title/abstract] OR cost effectiveness [Title/abstract] OR cost utility [Title/abstract] OR cost analysis [Title/abstract] OR Markov model [Title/abstract] OR cost [Title/abstract] OR costs [Title/abstract] OR economic [Title/abstract]) AND (screening [Title/abstract] OR endoscopy [Title/abstract] OR endoscopic [Title/abstract]) AND (stomach neoplasm [Title/abstract] OR gastric cancer [Title/abstract] OR *Helicobacter pylori* [Title/abstract] OR atrophy [Title/abstract] OR gastritis [Title/abstract] OR intestinal metaplasia [Title/abstract] OR dysplasia [Title/abstract])".

Cost Data

Costs were estimated from national sources for surveillance costs (endoscopy costs and related procedures if applicable including user fees but without administration related costs), health state costs (depending on stage of disease and corresponding treatments), adverse event costs (for endoscopic surveillance and for all gastric cancer treatments available) and indirect costs (working days lost and transportation). Resource use

such as frequency of visits to healthcare personnel was also included, but no assumptions were performed on other issues such as nurse time or time lost for relatives or caregivers.

Assumptions had to be made on costs for employers, and patients', and their families' expenses on transport, as no data were available for the Portuguese population. Employers' costs were based on the cost per hour reported by the Portuguese Institute of Statistics while transport expenses were based on a broad estimate of the distance between home and hospital for the general population [35]. Although productivity changes might occur, especially in cancer patients treated with surgery or during chemotherapy or radiotherapy treatments, the only assumptions were made on for employers' costs were for absence from work, but no changes in productivity were included in the model.

Utility Data

Health states and utilities for the Portuguese population and for patients with premalignant gastric conditions and adenocarcinoma were obtained with a single standardized health measurement instrument through a cross-sectional nationwide study of patients undergoing upper gastrointestinal endoscopy (n = 1434) in eight different hospitals including teaching, oncology, and regional hospitals (unpublished data). The EQ-5D-5L quality of life questionnaire (EuroQol) was used and reported in values that range from 0 (death) to 1 (optimal health) [36].

Patients were included without restrictive criteria and data were collected on age, gender, and presence of complaints. The patients were 52.6% male, 74.1% above 50 years of age, 47.3% without gastric lesions, 27.3% had premalignant conditions, and 10.3% had been or were being treated for gastric cancer. Results allowed adjustment for age and gender for inclusion in the present model.

Cost-Utility Analysis

The primary outcome measure for this economic evaluation was the incremental cost-effective ratio (ICER) between the endoscopic surveillance versus the no surveillance strategies, after a first endoscopy with a diagnosis of extensive premalignant conditions. Costs are included in the numerator and effectiveness in the denominator in terms of quality-adjusted life years (QALY). The willingness-to-pay was set at 50,000 US Dollars, as usual in most economic analyses and to allow for comparability to published studies, and converted to Euros (€) at a 2013 exchange rate to give a value of € 36,575 [37,38]. Other possibility for this controversial point could be the adoption of a threshold of twice the gross national income per capita as suggested by some institutions [39–41]. For Portugal that option would return a similar value: USD 41,240 or € 30,433 after conversion. To allow for comparability to other similar published studies, we adopted the same € 36,575 (USD 50,000) threshold.

Data on transition probabilities and range for both costs and outcomes are provided in Table 1 [13,15–17,22,35,42–64]. Every point estimate is accompanied by a range and a distribution to account for variability and allow sensitivity analysis, using deterministic and probabilistic approaches, and a half-cycle correction was used on all transitions in state, in both costs and outcomes. When proportions were not available for 1-year rates, nonannual probability was converted to an annual probability according to the formula [66]:

$$p_{\text{annual}} = 1 - ((1 - p_{\text{other year}})^{(1/p_{\text{other year}})})$$

As a secondary outcome, we also compared endoscopic surveillance for three different schedules (every 3, 5 and 10 years) versus the no surveillance alternative to analyze our option to model the 3-year schedule surveillance, as suggested by the guidelines [5].

For sensitivity analysis, when only a single value was available in the literature, that value was used for the base case and the range was calculated for a 10% deviation (5% below and 5% above the central value). This applied mainly to costs which are usually given by a single value in the literature.

For probabilistic analysis, all distributions had to be calculated using an approximation of the mean and standard deviation (SD) provided by the TreeAge software. For transition probabilities beta distributions were used with an alpha of $(\text{mean}^2)*(1-\text{mean})/(\text{SD}^2)$ and a beta of $((\text{mean}*(1-\text{mean})/(\text{SD}^2))-((\text{mean}^2)*(1-\text{mean})/(\text{SD}^2))$, and for costs gamma distributions were used with an alpha of $(\text{mean}^2)/(\text{SD}^2)$ and a lambda of $\text{mean}/(\text{SD}^2)$.

Expert opinion was sought in both the medical and economics areas for building the model and gathering the best available data but not for estimating any particular parameter.

Results

To ascertain if our model fitted real life, the Markov cohort of no surveillance was evaluated in a single-cycle period of 1 year and compared with real life numbers. The Portuguese population aged over 50 in 2011, taken from the last population records, was 4,044,816 individuals [35]. Assuming from a recent systematic

Table 1 Variables used in the Markov model for transition probabilities and costs

Variable	Base case value	Range for deterministic analysis		Distribution for probabilistic analysis	Source
Clinical data					
Proportions					
Male gender	0.61	0.58[a]	0.64[a]	Beta	[42]
Endoscopic bleeding	0.001	0.000	0.001	Beta	[43–45]
Endoscopic mortality	0.0001	0.0000	0.0001	Beta	[43]
Endoscopic specificity	0.97	0.97	1	Beta	[46]
Endoscopic perforation	0.0004	0.00009	0.0004	Beta	[16]
Endoscopy under anesthesia	0.12	0.06	0.18	Beta	[47]
ESD bleeding	0.066	0.063[a]	0.069[a]	Beta	[48]
ESD mortality	0.0086	0.0082[a]	0.0090[a]	Beta	[48]
ESD perforation	0.043	0.041[a]	0.045[a]	Beta	[48]
ESD recurrence	0.0105	0.010[a]	0.011[a]	Beta	[48]
Survival at 5 years if Stage I	0.80	0.56	1	Beta	[15]
Survival at 5 years if Stage II	0.50	0.37	0.71	Beta	[15]
Survival at 5 years if Stage III	0.30	0.11	0.48	Beta	[15]
Survival at 5 years if Stage IV	0.08	0.05	0.11	Beta	[15]
Progression from Premalignant to Cancer (annual)	0.005	0.0001	0.012	Beta	[16,49,50]
Progression from Premalignant to Dysplasia (annual)	0.017	0.004	0.083	Beta	[15,17,49]
Surgery after chemotherapy if stage III	0.84	0.79	0.89	Beta	[51]
Surgical mortality	0.089	0.052	0.16	Beta	[52]
Surgical complication	0.32	0.17	0.46	Beta	[53]
Surgical reoperation	0.08	0.009	0.18	Beta	[54,68]
Surgical bleeding	0.10	0.03	0.27	Beta	[53]
Surgical dehiscence	0.01	0.002	0.10	Beta	[53]
Surgical hernia	0.05	0.02	0.11	Beta	[53]
Patients at stage I in diagnosis	0.09	0.08[a]	0.10[a]	Beta	[16,55]
Patients at stage II in diagnosis	0.14	0.13[a]	0.15[a]	Beta	[16,55]
Patients at stage III in diagnosis	0.32	0.30[a]	0.34[a]	Beta	[16,55]
Patients at stage IV in diagnosis	0.45	0.43[a]	0.47[a]	Beta	[16,55]
Combined chemo and radiotherapy complication	0.48	0.46[a]	0.50[a]	Beta	[56]
Combined chemo and radiotherapy mortality	0.014	0.013[a]	0.015[a]	Beta	[56]
Combined chemo and radiotherapy treatment	0.50	0.47[a]	0.53[a]	Beta	[13]
Chemotherapy with Trastuzumab	0.22	0.20	0.36	Beta	[57]
Chemotherapy complication (Gastro)	0.24	0.23[a]	0.25[a]	Beta	[58]
Chemotherapy complication (Haemato)	0.20	0.19[a]	0.21[a]	Beta	[58]
Chemotherapy mortality	0.01	0.006	0.033	Beta	[59,60]
Recurrence after chemo and radiotherapy	0.29	0.23	0.34	Beta	[61]
Days lost for procedures or treatments					
Endoscopy	1	1[a]	2[a]	Gamma	Expert opinion
ESD	3	2[a]	4[a]	Gamma	Expert opinion
ESD complication	3	2[a]	4[a]	Gamma	Expert opinion
Surgery (in hospital)	10	8.4	18.8	Gamma	[68]
Surgery (recover at home)	10	9[a]	11[a]	Gamma	Expert opinion
Surgery complication	5	4[a]	6[a]	Gamma	Expert opinion
Chemotherapy with ECF	90	86[a]	94[a]	Gamma	Expert opinion
Chemotherapy with De Gramont	80	76[a]	84[a]	Gamma	Expert opinion
Chemotherapy with LV5FU2	120	114[a]	126[a]	Gamma	Expert opinion
Chemotherapy complication	3	2[a]	4[a]	Gamma	Expert opinion
Radiotherapy complication	3	2[a]	4[a]	Gamma	Expert opinion
Radiotherapy	25	24[a]	26[a]	Gamma	Expert opinion
Palliative treatment	50	47[a]	53[a]	Gamma	Expert opinion
Cost data					
Discount	0.03	0.00	0.05	Beta	[22]
Working day	52	46[a]	58[a]	Gamma	[35]
Transport between home and hospital	2.5	0	25	Gamma	Expert opinion

(Continued)

Table 1 (Continued)

Variable	Base case value	Range for deterministic analysis		Distribution for probabilistic analysis	Source
Anesthesia	183	174[a]	192[a]	Gamma	[62]
Appointment	31	29[a]	33[a]	Gamma	[62]
Endoscopy biopsy	28	27[a]	29[a]	Gamma	[62]
Cancer staging	282	268[a]	296[a]	Gamma	[62]
Cancer staging with EUS	102	97[a]	107[a]	Gamma	[62]
Cancer staging with PET scan	1033	981[a]	1085[a]	Gamma	[62]
Cancer surveillance	205	195[a]	215[a]	Gamma	[62]
PICC placement	75	71[a]	79[a]	Gamma	[62]
PICC removal	48	46[a]	50[a]	Gamma	[62]
PICC if chemotherapy with ECF	122	116[a]	128[a]	Gamma	[63]
PICC if chemotherapy with De Gramont	153	145[a]	161[a]	Gamma	[63]
PICC if chemotherapy with LV5FU2	229	218[a]	240[a]	Gamma	[63]
Endoscopy	60	57[a]	63[a]	Gamma	[62]
Endoscopic clipping	203	193[a]	213[a]	Gamma	[62]
Endoscopic hemorrhage	13	12[a]	14[a]	Gamma	[62]
Endoscopic injection	34	32[a]	36[a]	Gamma	[62]
ESD	933	886[a]	980[a]	Gamma	[62]
Surgery	1909	1814[a]	2004[a]	Gamma	[62]
Surgery biopsy	315	299[a]	331[a]	Gamma	[62]
Surgery complicated	4531	4304[a]	4758[a]	Gamma	[62]
Chemotherapy with ECF	237	225[a]	249[a]	Gamma	[63]
Combined chemotherapy and radiotherapy	139	132[a]	146[a]	Gamma	[63]
Chemotherapy with LV5FU2	347	330[a]	364[a]	Gamma	[63]
Chemotherapy with Trastuzumab	16,306	15,491[a]	17,121[a]	Gamma	[63]
Radiotherapy	2723	2587[a]	2859[a]	Gamma	[62]
In-patient daily if Surgery	408	388[a]	428[a]	Gamma	[64]
In-patient daily if Oncology	382	363[a]	401[a]	Gamma	[64]
In-patient daily if Radiotherapy	143	136[a]	150[a]	Gamma	[64]
In-patient daily if Palliative treatment	326	310[a]	342[a]	Gamma	[64]
User fee for endoscopy	12	11[a]	13[a]	Gamma	[64]
User fee for endoscopic biopsy	5	4.5[a]	5.5[a]	Gamma	[64]
User fee for endoscopic clipping	20	19[a]	21[a]	Gamma	[64]
User fee for endoscopic injection	6	5.5[a]	6.5[a]	Gamma	[64]
User fee for Anesthesia	29	28[a]	30[a]	Gamma	[64]
User fee for ESD	20	19[a]	21[a]	Gamma	[64]
Utility data					
Cancer if female	0.70	0.42	0.97	Beta	unpublished data
Cancer if male	0.66	0.49	0.83	Beta	unpublished data
ESD if female	0.70	0.33	1	Beta	unpublished data
ESD if male	0.77	0.50	1	Beta	unpublished data
Premalignant condition if female	0.70	0.66	0.74	Beta	unpublished data
Premalignant condition if male	0.82	0.79	0.85	Beta	unpublished data
Chemo or radiotherapy if female	0.76	0.60	0.92	Beta	unpublished data
Chemo or radiotherapy if male	0.85	0.79	0.91	Beta	unpublished data
Surgery if female	0.71	0.62	0.80	Beta	unpublished data
Surgery if male	0.79	0.72	0.87	Beta	unpublished data

All variables have a value for the base case scenario plus a range for inclusion in deterministic one-way sensitivity analysis and distributions for the probabilistic Monte Carlo sensitivity analysis.

ESD, Endoscopic submucosal dissection; EUS, endoscopic ultrasonography; PET, positron emission tomography; PICC, peripherally inserted central catheter; ECF, epirubicin, cisplatin and fluorouracil; LV5FU2, fluorouracil, folinic acid and cisplatin; de Gramont, fluorouracil and folinic acid.

[a]Range not available in published literature and calculated for a 10% deviation (5% below and 5% above the base case value).

review of studies on the prevalence of premalignant lesions that 20% of them have premalignant gastric conditions [66] (808,963 individuals), when these patients are input in the model it gives 0.28% for cancer cases. This means 3316 gastric cancer cases per year, very similar to the real life estimates of 3018 gastric

cancer cases in Portugal, according to the GLOBOCAN 2012 estimates [42].

The results of the model for the base case scenario were also compared with the three schedules (every 3, 5, or 10 years) of endoscopic surveillance versus no surveillance and are displayed in Table 2. It shows that, if all surveillance strategies after a first endoscopy are compared against the same common no-surveillance baseline, the 3-yearly endoscopic surveillance provides incremental effectiveness with more QALY at the cost of increasing costs while surveillance every 5 or 10 years are dominated by providing less effectiveness at increased costs. The ICER of endoscopic surveillance every 3 years is € 18,366 per QALY with a discount of 3% (€ 14,223 with a discount of 5%), well below the defined threshold of willingness-to-pay, which is € 36,575 (and also below the €30,433 threshold if the option based on the gross national income). The plot of the three endoscopic surveillance options versus the no surveillance strategy is given in Fig. 2. The cost-effectiveness frontier is represented by the line between the no-surveillance baseline and the endoscopic surveillance every 3 years, while the 5- and the 10-year endoscopic schedules are to the left of the cost-effectiveness frontier, being dominated by the 3-yearly alternative.

For the one-way deterministic sensitivity analysis, the influence on the ICER is shown in Fig. 3 as a tornado diagram. Variables are listed from top to bottom, from the most influential parameter to the least, and variables not shown had even less influence on the ICER. Variables that most influenced the ICER were the proportion of males or females affected by the disease relative to other important variables such as utilities that differ between genders and to the proportion of patients

Table 2 Base case results of endoscopic surveillance versus no surveillance in different schedules

Endoscopic surveillance	Cost (€)	Incremental cost (€)	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost/Effectiveness (€/QALY)	Incremental cost/Effectiveness ratio (ICER) (€/QALY)
No	130		13.607		10	
Every 3 years	1584	1454	13.687	0.079	116	18,336
Every 5 years	1494	1363	13.565	−0.042	110	(Dominated)
Every 10 years	1818	1688	13.268	−0.339	137	(Dominated)

Endoscopic surveillance every 3 years provides incremental effectiveness with more QALY at the expense of higher costs, while surveillance every 5 or 10 years is clearly provides less effective and more expensive.
€, Euros; QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio.

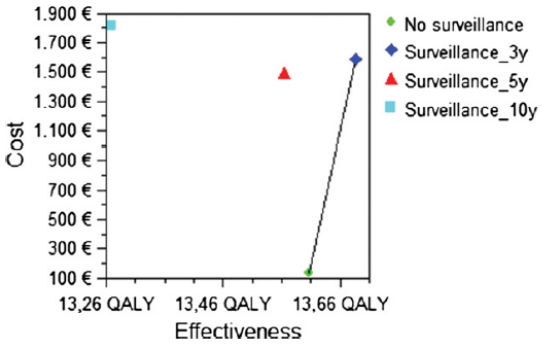

Figure 2 Cost-effectiveness analysis of endoscopic surveillance every 3, 5, and 10 years versus no surveillance. Cost-effectiveness analysis comparing three different endoscopic surveillance strategies, where the *x*-axis represents the effectiveness in quality-adjusted life years (QALY) and the *y*-axis represents the cost in Euros (€). The cost-effectiveness frontier is presented by the line between the no-surveillance baseline and endoscopic surveillance every 3 years, while the 5- and 10-year endoscopic schedule is to the left of the cost-effectiveness frontier, being dominated by providing less effectiveness.

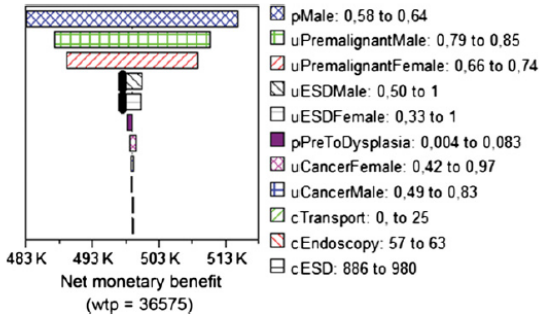

Figure 3 Tornado diagram for deterministic one-way sensitivity analysis. Variables tested in one-way sensitivity analysis are displayed on the *x*-axis while the dotted line on the *x*-axis represents the base case value in terms of net monetary benefit in Euros for a willingness-to-pay (WTP) of € 36,575, with variables having the widest range for the final result with a wider line at the top. Variables are followed by the values of their analytical range. Variables not displayed varied even less from the result of the model. K – thousand, *p* – probability, u – utility, c – cost, PreToDysplasia – progression from premalignant lesion to dysplasia.

Table 3 Deterministic one-way sensitivity analysis results of endoscopic surveillance every 3 years versus no surveillance

Variable	Range for sensitivity analysis		Change in incremental cost-effectiveness ratio (ICER)	
	Lower value	Higher value		
Proportion of male	0.58	0.64	18,841	17,857
Utility if Premalignant condition if male	0.79	0.85	17,410	19,366
Utility if Premalignant condition if female	0.66	0.74	17,541	19,207
Utility if ESD if male	0.50	1.00	42,875	12,326
Progression from premalignant to dysplasia	0.004	0.083	13,684	31,887
Utility if ESD if female	0.33	1.00	36,779	13,036
Utility if cancer if female	0.42	0.97	20,318	16,032
Utility if cancer if male	0.49	0.83	19,071	17,655
Cost of transport	0	25	17,909	20,044
Cost of ESD	886	980	18,173	18,499
Cost of endoscopy	57	63	18,117	18,555
Cost of anesthesia	174	192	18,223	18,449
Proportion of endoscopies under anesthesia	0.06	0.18	17,535	19,137
Cost of surgery	1814	2004	18,302	18,370
Cost of radiotherapy	2587	2859	18,317	18,355
Cost of cancer staging	268	296	18,332	18,340
Cost of chemotherapy	15,491	17,121	18,342	18,330
Cost of working day	46	58	17,762	18,909

ESD, Endoscopic submucosal dissection.

progressing from premalignant conditions to dysplasia. In terms of cost, the most influential variable was the cost of transport, which was even more relevant than all the usually used medical costs such as endoscopy, anesthesia, surgery, chemotherapy, and radiotherapy. In Table 3, the same variables are displayed along with

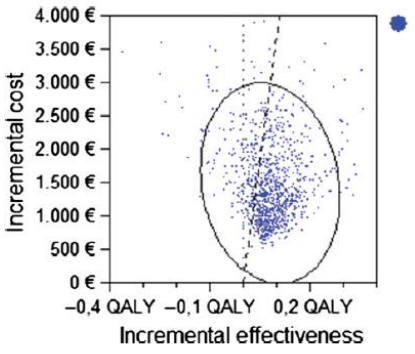

Figure 4 Scatter plot for probabilistic Monte Carlo sensitivity analysis of the endoscopic surveillance every 3 years versus no surveillance. Scatter plot representing 1000 simulations in a Monte Carlo probabilistic sensitivity analysis where the *x*-axis represents incremental effectiveness in terms of quality-adjusted Life years (QALY) and the *y*-axis represents incremental costs in Euros. The ellipse surrounds the estimates that fall within the 95% confidence intervals. Cost-effective simulations are on the right-hand side and below the dotted line representing the willingness-to-pay threshold, set at € 36,575 and comprise 78% of all simulations.

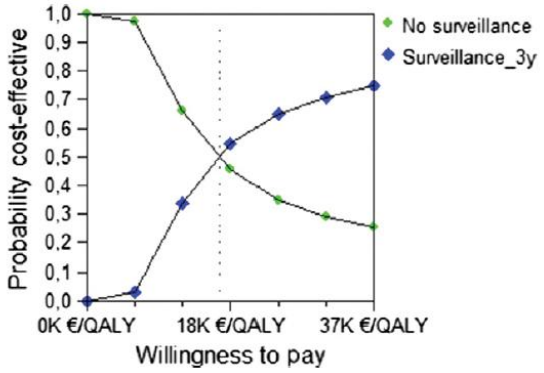

Figure 5 Acceptability curve of the endoscopic surveillance every 3 years versus no surveillance. Acceptability curves comparing both strategies, where the *x*-axis represents the willingness-to-pay in Euros per quality-adjusted life years (QALY) and the *y*-axis represents the probability of cost-effectiveness, ranging from 0 to 100%. The intersection represents the point where, for a willingness-to-pay value of € 18,336 per QALY, the option for endoscopic surveillance every 3 years has a probability of 50% to be cost-effective compared with the absence of surveillance, well below the threshold of € 36,575; the higher the threshold is, the higher is the probability that the surveillance is cost-effective. K – thousand.

their influence on the ICER, showing that although the ICER changes, it is always below the adopted threshold except for the lowest ranges of utility of patients submitted to endoscopic submucosal dissection.

The results for Monte Carlo probabilistic analysis are displayed in Fig. 4 as an ICER scatter plot. For 1000 repetitions and a threshold of € 36,575 (corresponding to USD 50,000), the analysis shows that endoscopic surveillance every 3 years was cost-effective in 78% of cases with a discount of 3% (85% with a discount of 5%), represented by all points on the right-hand side and in the section below the dotted line of the willingness-to-pay threshold. The corresponding acceptability curve in Fig. 5 shows that at € 18,336 per additional QALY, the 3-year surveillance strategy has a probability of 50% to be cost-effective compared with the absence of surveillance; the higher the threshold is, the higher is the probability that the surveillance is cost-effective.

Discussion

One way to improve the survival rate of gastric cancer patients is to increase detection of lesions in an early stage. That could be accomplished by the surveillance of high-risk patients with extensive premalignant conditions at risk of progressing to invasive cancer. An endoscopic surveillance schedule of every 3 years was suggested in recent guidelines on a clinical basis but there is a lack of adequate study to show that this approach is cost-effective [5–7].

We modeled that clinical option and found that our model fitted real life estimates and that it is cost-effective to follow patients by endoscopy every 3 years if they present extensive premalignant conditions detected at start by an opportunistic screening endoscopy with biopsies. Our model shows an incremental cost-effectiveness ratio of only € 18,336 per QALY, well below the

Table 4 Published models of economic studies on endoscopic surveillance of premalignant conditions versus no surveillance, compared with the present study

Study (1st author, publication year)	Present study	Dinis-Ribeiro (2007)	Hassan (2010)	Yeh (2010)
Type of study	Cost-utility	Cost-utility	Cost-effectiveness	Cost-utility
Country/Model year	Portugal, 2013	Portugal, Unknown	USA, 2008	USA, 2007
Intervention	Endoscopy every 3 years	Chromoendoscopy every 1 year	Endoscopy every 1 year	Endoscopy every 10 years
Perspective	Societal	Health service	Health service	Societal
Threshold/Unit	50,000 US dollars (36,575 Euros)	Unknown Euros	100,000 US dollars	50,000 US dollars
Population	Extensive premalignant lesions	Extensive premalignant lesions	Intestinal metaplasia	Intestinal metaplasia
Sensitivity analysis	One-way, Probabilistic	One-way	Two-way, Probabilistic	One-way, Probabilistic
Source of effectiveness	LYS, QALY	QALY	LYS	QALY
Result (ICER)	18,336 € per QALY	1868 € per QALY	72,519 USD per LYS	544,500 USD per QALY
Relevant variables in sensitivity analysis	Utilities	Quality of life after surgery	Cancer incidence reduction	Surgical risks
	Gender proportion	Chemotherapy cost	Cancer down-staging	Success of endoscopic resection
Strengths/Limitations	Strengths:	Limitations:	Limitations:	Limitations:
Type of review	Systematic review	Not detailed	Not detailed	Not detailed
Model complexity	Extensive	Simple	Simple	Simple
Number of variables (clinical, cost)	Extensive [36,56]	Small [3,6]	Small [2]	Moderate [10,25]
Utilities	Utilities from specific population	Utilities from other populations	No utilities	Utility valuations not detailed
Threshold	According to guidelines	Not detailed	Not conventional	
Conclusion	Endoscopy every 3 years is cost-effective for extensive atrophy or intestinal metaplasia	Chromoendoscopy every 1 year is cost-effective for extensive atrophy or intestinal metaplasia	Endoscopy every 1 year is cost-effective for intestinal metaplasia	Endoscopy every 10 years is not cost-effective for intestinal metaplasia

USA, United States of America; LYS, life years saved; QALY, quality-adjusted Life years; ICER, incremental cost-effectiveness ratio.

usual willingness-to-pay threshold of USD 50,000 (equal to € 36,575 at a 2013 exchange rate and also below the €30,433 threshold if the option based on the gross national income) while surveillance at every 5 or 10 years was dominated as they provide less effectiveness (probably due to the increased cases of advanced gastric cancer) at similar costs (less costs on surveillance but more costs for advanced disease treatments).

The results of our study proved to be robust also in sensitivity analyses, as variables evaluated by a one-way deterministic analysis remained below the threshold in all cases even in the extremes of the range used, except for utilities of patients submitted to endoscopic submucosal dissection but only at the lowest range, even below the utility of patients with present cancer. Furthermore, the Monte Carlo probabilistic analysis revealed that even when simulating all variables together, in 78% of cases the ICER would fall below the willingness-to-pay threshold.

Table 4 presents a comparison of our study and the available literature, which comprises only three published models whose results disagree [15–17]. Modeling has evolved considerably since the first study was published in 2007 by Dinis-Ribeiro et al. [15], but we think our model has some strengths that serve to enrich our conclusions and help explain the discrepancies in the conclusions published so far. Not all the studies adopted a cost-utility calculation that incorporated QALY and a societal perspective by including the cost to patients and to employers, as ours does. In fact, our study is the only one to use utilities specific to the population included, rather than adopting preferences from the literature but from different populations. The references used for the variables are supported in a previously published systematic review [7] and most references are from systematic not single studies as the other models did, which might not be the best available estimate. The model described here is much more detailed than the previous studies, all but three references used for clinical data are from the 5 years immediately before the year considered in the model, and we have included in the sensitivity analysis the full range of the three earlier models. In terms of progression rates, they proved to be relevant to the sensitivity analysis, probably explaining to some extent the differences in the published results. We think that by doing so we have accomplished a level 1b economic study according to the Oxford levels of evidence, by providing an "analysis based on clinically sensible costs or alternatives with a systematic review of the evidence and including multiway sensitivity analyses" [67].

There are, however, some limitations in the present study. Although the model is extensive, it does not definitely accommodate all possible clinical real life options, and it is impossible to know how far or how near we are to the perfect model. Also, even using utilities obtained directly from the studied population, the utilities valuation is also open to bias and the confidence intervals available are large. Ranges and distributions for sensitivity analysis are not generally available in the literature and the approximations we used might not be the best option and finally the model was conceived with data for the Portuguese population and adjustments would need to be made in other countries, namely on costs, to prove its generalisability.

In conclusion, the endoscopic surveillance every 3 years of patients at high risk for gastric cancer, as they present conditions such as extensive atrophy or intestinal metaplasia in the corpus in a previous endoscopy, is cost-effective. Studies evaluating the impact of this option are needed to confirm if it will improve early gastric cancer detection rates, increase curative endoscopic resections, detect invasive cancer in earlier stages, and ultimately lead to better overall survival for gastric cancer patients.

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Chapter V - Discussion

Improving survival of gastric cancer patients might be achieved by increasing the detection of lesions in an earlier stage and that goal could be accomplished by the surveillance of high-risk patients with extensive premalignant conditions at risk of progressing to invasive cancer. An endoscopic surveillance schedule every 3-years was suggested in recent guidelines on a clinical basis but better studies are needed to show its cost-effectiveness (Areia, Carvalho, Cadime, Rocha Goncalves, & Dinis-Ribeiro, 2013; Dinis-Ribeiro, Areia et al., 2012; Dinis-Ribeiro, Areia et al., 2012).

The objective of the present thesis was to determine the cost-utility of this endoscopic surveillance every 3 years in patients with extensive gastric premalignant conditions compared with no surveillance. To accomplish that goal we first performed two systematic reviews and one cross-sectional study in order to obtain the best available clinical data for the Portuguese population and then a cost-utility economic analysis on this hypothesis.

Preliminary studies

With our first systematic review of studies on the subject of cost-effectiveness of gastric cancer screening or surveillance, we think to have accomplished the objective of obtaining the best available evidence published so far (Areia, Carvalho, Cadime, Rocha Goncalves, & Dinis-Ribeiro, 2013). That information was very helpful for the conception of our model and also by providing both strengths and weaknesses of the available evidence.

We concluded that endoscopy was more cost-effective than no screening but depended mainly on its cost (Dan, So, & Yeoh, 2006; Gupta, Bansal et al., 2011; Tashiro, Sano, Kinameri, Fujita, & Takeuchi, 2006; Zhou, Guan et al., 2011). When different schedule options for endoscopic screening were analyzed, the ICER results would vary but still remain below the USD 50,000 threshold. These results were in accordance with a recent endoscopic screening study from a high-risk population in Korea that concluded that endoscopic intervals of 3 years or below showed similar protective benefits in relation to the detection of an advanced gastric cancer stage disease (Nam, Choi et al., 2012). This result supports our option on modelling the cost-effectiveness of endoscopy instead of other technologies.

We also concluded that in respect of endoscopic follow-up of patients with premalignant conditions the available evidence was contradictory and limited to 3 studies, with one European model claiming that the surveillance of patients with extensive atrophy or intestinal metaplasia was cost-effective (Dinis-Ribeiro, da Costa-Pereira, Lopes, & Moreira-Dias, 2007) whilst a model for the American population with intestinal metaplasia concluded that surveillance presented a ICER that was above the usually accepted threshold in most economic analyses (Hassan, Zullo et al., 2010). A third model, also for the American population, concluded that endoscopy was cost-effective only in patients with dysplasia but not for intestinal metaplasia (Yeh, Hur, Kuntz, Ezzati, & Goldie, 2010). These conflicting results seemed to be related to different assumptions on the progression or regression of conditions, assessment of extension of premalignant conditions, estimates for the 5-year stage specific mortality but also on costs of endoscopy and dissimilar populations. These results showed that this field of endoscopic surveillance of premalignant conditions clearly needed more

economic studies, models and better scientific evidence, further supporting the aim of the present thesis.

Finally, we also concluded that the published studies presented several problems according to the guidelines suggestions (Drummond & Jefferson, 1996), that we have identified and would not want to repeat in our model, such as: models not using the "no action" option in the reference case (Tashiro, Sano, Kinameri, Fujita, & Takeuchi, 2006), only three articles adopting the societal perspective recommended (Y. C. Lee, Lin et al., 2007; Yeh, Hur, Kuntz, Ezzati, & Goldie, 2010; Yeh, Kuntz, Ezzati, & Goldie, 2009), only one third of the studies using both length of time (LYS) and quality of that time (QALY) as effectiveness estimates, and most studies using patient preferences instead of the recommended community preferences (Dan, So, & Yeoh, 2006; Dinis-Ribeiro, da Costa-Pereira, Lopes, & Moreira-Dias, 2007; Gupta, Bansal et al., 2011; Xie, Luo, Blackhouse, Goeree, & Lee, 2008; Xie, Luo, & Lee, 2008; Xie, O'Reilly et al., 2009; Yeh, Hur, Kuntz, Ezzati, & Goldie, 2010; Yeh, Kuntz, Ezzati, & Goldie, 2009; Zhou, Guan et al., 2011).

With our second systematic review we think to have provided the first systematic review and meta-analysis on the global prevalence of gastric premalignant conditions published so far and their relation with the gastric cancer incidence of the studied population (Marques-Silva, Areia, Elvas, & Dinis-Ribeiro, 2014). The result on the prevalence of extensive conditions would be very helpful by providing further evidence on this prevalence rate and allowing some validation of our final model estimates versus real life values.

We concluded that the prevalence of extensive gastric premalignant conditions was only 7% in countries with low to moderate incidence of gastric cancer but in countries with high incidence such as Portugal it reached 16% for extensive intestinal metaplasia and 27% for extensive atrophy. These estimates reinforced the relevance of this prevalence rate of patients harbouring a high-risk phenotype to which endoscopic surveillance could be offered, as we wanted to model in our thesis.

With our cross-sectional study we obtained health utilities from a Portuguese population that included patients without gastric lesions, with all sorts of upper gastrointestinal diseases, all ranges of premalignant gastric conditions and also with gastric cancer, submitted to all available treatments, including endoscopic, surgery, chemotherapy, radiotherapy or just best supportive care (Areia, Alves et al., 2014). This information was essential to the development of our final model by allowing the construction of a cost-utility model instead of a cost-effective one. Also, the utility data obtained, specific for the Portuguese, would be just perfect for a model idealized for the Portuguese population and would provide utility values for all disease stages necessary for building the model.

We concluded that health utilities measured by the EQ-5D-5L questionnaire was feasible and showed similar scores for patients without gastric lesions (0.78), patients with premalignant conditions (0.82) and patients with previously treated gastric cancer (0.77-0.79) but lower values for patients with present carcinoma (0.66) and that, for the same clinical situations, EQ-5D-5L scores were always lower for female than for male. This conclusion was very important for the final economic results of our model by pointing out the fact that utilities may not vary so much between different clinical

situations along the gastric carcinogenesis cascade as suggested by other published studies, and that wider published values in the available literature might have resulted from the use of different questionnaires in different clinical situations. Also, male and female provided different perceptions of utility for the same situations and that result should be incorporated in our final model.

We also compared our results to the published studies used in previous cost-utility analysis and concluded that several problems existed within the methodology of the published literature that we think to have overcome with the present study. Examples of such problems detected: no values for the asymptomatic population (Dan, So, & Yeoh, 2006; Dinis-Ribeiro, da Costa-Pereira, Lopes, & Moreira-Dias, 2007; Gupta, Bansal et al., 2011; Xie, Luo, Blackhouse, Goeree, & Lee, 2008; Xie, Luo, & Lee, 2008; Xie, O'Reilly et al., 2009; Zhou, Guan et al., 2011); use of 1 as the value for the normal population (Xie, Luo, Blackhouse, Goeree, & Lee, 2008; Zhou, Guan et al., 2011); only one study had values for gastric premalignant conditions (Yeh, Hur, Kuntz, Ezzati, & Goldie, 2010); only one study had values for the post mucosectomy stage (Dinis-Ribeiro, da Costa-Pereira, Lopes, & Moreira-Dias, 2007); only two models presented more than a single value for all gastric cancer patients, irrespective of type of treatment performed (Dan, So, & Yeoh, 2006; Dinis-Ribeiro, da Costa-Pereira, Lopes, & Moreira-Dias, 2007) and finally only two authors used a single reference to obtain the utilities for their models: the study by Wang Q et al (Wang, Jin, Lin, Xu, & Chen, 2003) that is in Chinese and not available to most clinicians, and the study by Dinis-Ribeiro et al (Dinis-Ribeiro, da Costa-Pereira, Lopes, & Moreira-Dias, 2007) that used a systematic review of studies embracing several different questionnaires on patients with diagnosed or treated gastric cancer.

Cost-utility model

When modelling the strategy of endoscopic surveillance of patients with extensive premalignant lesions by endoscopy every 3 years, we concluded that it was cost-effective (Areia, Dinis-Ribeiro, & Rocha Goncalves, 2014).

We concluded that our model showed an incremental cost effectiveness ratio (ICER) of only € 18,336 per QALY, well below the usual willingness-to-pay threshold of USD 50,000, equal to € 36,575 at a 2013 exchange rate and also below the € 30,433 threshold if the option was based on the gross national income (Shillcutt, Walker, Goodman, & Mills, 2009).

Surveillance at every 5 or 10 years were dominated as they provided less effectiveness (probably due to the increased cases of advanced gastric cancer) at similar costs (less costs on surveillance but more costs for advanced disease treatments). This confirmed our clinical perception that was published in the guidelines (Dinis-Ribeiro, Areia et al., 2012) that a 3-year interval seemed to be in good balance between a very intensive surveillance (possible increase detection at an increased cost) and a more spaced surveillance that might be losing early lesions (and decreasing effectiveness).

We also concluded that the results were robust in sensitivity analyses, as variables evaluated by one-way deterministic analysis remained below the threshold in all cases even in the extremes of the range used, except for utilities of patients submitted to endoscopic submucosal dissection but only at an unrealistic lowest range, even below the utility of patients with present cancer.

Furthermore, the Monte Carlo probabilistic analysis revealed that even when simulating all variables together, in 78% of simulations the ICER would fall below the willingness-to-pay threshold. These results further support our conclusion that an endoscopic surveillance every 3 years in this specific population was cost-effective.

Modelling has evolved considerably since the first study on surveillance of patients with extensive conditions was published in 2007 by Dinis-Ribeiro et al (Dinis-Ribeiro, da Costa-Pereira, Lopes, & Moreira-Dias, 2007) but we think our model has some strengths that serve to enrich our conclusions and help explain the discrepancies in the conclusions published so far.

Not all the studies adopted a cost-utility calculation that incorporated QALY and a societal perspective by including the cost to patients and to employers, as ours does. In fact, our study is the only one to use utilities specific to the population included, rather than adopting preferences from the literature but from different populations (Areia, Alves et al., 2014). The references used for the variables are supported in a previously published systematic review (Areia, Carvalho, Cadime, Rocha Goncalves, & Dinis-Ribeiro, 2013) and most references are from systematic not single studies as the other models did, which might not be the best available estimate.

Our model was also much more detailed than the previous studies, all but three references used for clinical data were from the 5 years immediately before the year considered in the model, and we have included in sensitivity analysis the full range of progression rates from the 3 earlier models which proved to be relevant to the sensitivity analysis.

We think that by doing so we have accomplished a level 1b economic study according to the Oxford Levels of Evidence, by providing an "analysis based on clinically sensible costs or alternatives with a systematic review of the evidence and including multi-way sensitivity analyses" (Oxford, 2011).

A comparison of our model with the available literature, which comprises only 3 published models whose results disagree, is presented in **Table 5** (Dinis-Ribeiro, da Costa-Pereira, Lopes, & Moreira-Dias, 2007; Hassan, Zullo et al., 2010; Yeh, Hur, Kuntz, Ezzati, & Goldie, 2010).

Table 5 Published models of economic studies on endoscopic surveillance of premalignant conditions versus no surveillance, compared to the present thesis

Study (1st author, publication year)	**Present thesis 2013**	**Dinis-Ribeiro 2007**	**Hassan 2010**	**Yeh 2010**
Type of study	Cost-utility	Cost-utility	Cost-effectiveness	Cost-utility
Country / Model	Portugal	Portugal	USA	USA
Year	2013	2005	2008	2007
Intervention	Endoscopy every 3 years	Chromoendoscopy every 1 year	Endoscopy every 1 year	Endoscopy every 10 years
Perspective	Societal	Health service	Health service	Societal
Threshold / Unit	USD 50,000 (36,575 Euros)	Euros 50,000	USD 100,000	USD 50,000
Population	Extensive premalignant lesions	Extensive premalignant lesions	Intestinal metaplasia	Intestinal metaplasia
Sensitivity analysis	One-way, Probabilistic	One-way	Two-way, Probabilistic	One-way, Probabilistic
Source of Effectiveness	LYS, QALY	QALY	LYS	QALY
Result (ICER)	€ 18,336 per QALY	€ 1,868 per QALY	USD 72,519 per LYS	USD 544,500 per QALY
Relevant variables in sensitivity analysis	Utilities	Quality of life after surgery	Cancer incidence reduction	Surgical risks
	Gender proportion	Chemotherapy cost	Cancer down-staging	Success of endoscopic resection
Strengths / Limitations	***Strengths:***	***Limitations:***	***Limitations:***	***Limitations:***
Type of review	Systematic review	Not detailed	Not detailed	Not detailed
Model complexity	Extensive	Simple	Simple	Simple
Number of variables (clinical, cost)	Extensive (58, 38)	Small (3, 6)	Small (7, 2)	Moderate (25, 10)
Utilities	Utilities from specific population	Utilities from other populations	No utilities	Utility valuations not detailed
Threshold	According to guidelines	Not detailed	Not conventional	
Conclusion	Endoscopy every 3 years is cost-effective for extensive atrophy or intestinal metaplasia	Chromoendoscopy every 1 year is cost-effective for extensive atrophy or intestinal metaplasia	Endoscopy every 1 year is cost-effective for intestinal metaplasia	Endoscopy every 10 years is not cost-effective for intestinal metaplasia

Legend: USA- United States of America, LYS- Life years saved, QALY- Quality adjusted Life years, ICER- Incremental cost effectiveness ratio, USD- United States Dollars.

There are, however, some limitations in the present model. Although it is extensive, it does not definitely accommodate all possible clinical real life options, and it is impossible to know how far or how near we are to the perfect model. Also, even by using utilities obtained directly from the studied population, the utilities valuation is also open to bias and the confidence intervals available are wide (Areia, Alves et al., 2014). Finally, the ranges and distributions for sensitivity analysis are not generally available in the literature and the approximations we used might not be the best option.

Chapter VI - Conclusion and Further Research

Conclusion

In conclusion, according to our model, endoscopic surveillance of patients with premalignant conditions such as extensive atrophy or intestinal metaplasia, every 3 years, in an intermediate-risk country such as Portugal, is cost-effective.

This strategy provides an incremental cost effectiveness ratio of only € 18,336 per QALY, well below the usual willingness-to-pay threshold of € 36,575 (equivalent to USD 50,000) and also below € 30,433 if the threshold was based on the gross national income, while surveillance at every 5 or 10 years were dominated as they provided less effectiveness at similar costs.

Our model fitted real life estimates and proved to be robust in sensitivity analyses, as almost all variables evaluated in one-way deterministic analysis remained below the threshold and in Monte Carlo probabilistic analysis 78% of simulations would fall below the willingness-to-pay threshold.

Further research

Further studies evaluating the impact of this option are needed to confirm if surveillance will in fact improve early gastric cancer detection rates, increase curative endoscopic resections, detect invasive cancer in earlier stages and ultimately lead to better overall survival for gastric cancer patients.

The hypothesis modelled in the present thesis should be replicated in other countries in order to confirm or not its cost-utility in other populations, particularly in countries with only low to moderate gastric cancer incidence.

Moreover, effectiveness could be further studied in terms of monetary benefits by transforming health benefits in monetary units and performing a cost-benefit analysis, along the cost-utility analysis.

Finally, screening instead of surveillance could be modelled in a similar manner, to decide if in a specific population it would be cost-effective to screen instead of surveillance and in which specific high-risk population could this strategy be offered.

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